2018

Association between blood eosinophil count and risk of readmission for patients with asthma: historical cohort study

Jones, Rupert

10.1371/journal.pone.0201143
PLoS ONE
Public Library of Science

PLOS ONE

Association between blood eosinophil count and risk of readmission for patients with asthma: historical cohort study

--Manuscript Draft--

Manuscript Number:	PONE-D-18-12337R1
Article Type:	Research Article
Full Title:	Association between blood eosinophil count and risk of readmission for patients with asthma: historical cohort study
Short Title:	Blood eosinophil count and risk of readmission for asthma
Corresponding Author:	David B Price Observational & Pragmatic Research Institute Paya Lebar Square, SINGAPORE
Keywords:	asthma; eosinophils; hospitalization; patient readmission
Abstract:	Background Recent studies have demonstrated an association between high blood eosinophil counts and greater risk of asthma exacerbations. We sought to determine whether patients hospitalized for an asthma exacerbation were at greater risk of readmission if they had a high blood eosinophil count documented before the first hospitalization. Methods This historical cohort study drew on 2 years of medical record data (Clinical Practice Research Datalink with Hospital Episode Statistics linkage) of patients (aged ≥5 years) admitted to hospital in England for asthma, with recorded blood eosinophil count within 1 baseline year before admission. We analyzed the association between high blood eosinophil count (≥0.35x109 cells/L) and readmission risk during 1 year of follow-up after hospital discharge, with adjustment for predefined, relevant confounders using forward selection. Results We identified 2,613 eligible patients with asthma-related admission, of median age 51 years (interquartile range, 36-69) and 76% women (1,997/2,613). Overall, 835/2,613 (32.0%) had a preadmission high blood eosinophil count. During the follow-up year, 130/2,613 patients (5.0%) were readmitted for asthma, including 55/835 (6.6%) with vs. 75/1,778 (4.2%) without high blood eosinophil count at baseline (adjusted hazard ratio [HR] 1.49; 95% CI 1.04-2.13, p=0.029). The association was strongest in never-smokers (n=1,296; HR 2.16, 95% CI 1.27-3.68, p=0.005) and absent in current smokers (n=547; HR 1.00, 95% CI 0.49-2.04, p=0.997). Conclusions A high blood eosinophil count in the year before an asthma-related hospitalization is associated with increased risk of readmission within the following year. These findings suggest that patients with asthma and preadmission high blood eosinophil count require careful follow-up, with treatment optimization, after discharge.
Order of Authors:	Marjan Kerkhof
	Trung N Tran
	Maarten van den Berge
	Guy G Brusselle
	Gokul Gopalan
	Rupert CM Jones
	Janwillem WH Kocks
	Andrew Menzies-Gow
	Javier Nuevo
	Ian D Pavord
	Sarang Rastogi

	David B Price
Opposed Reviewers:	
Response to Reviewers:	Response to reviewers file uploaded with revised files
Additional Information:	
Question	**Response**
Financial Disclosure Please describe all sources of funding that have supported your work. **This information is required for submission and will be published with your article, should it be accepted.** A complete funding statement should do the following: Include **grant numbers and the URLs** of any funder's website. Use the full name, not acronyms, of funding institutions, and use initials to identify authors who received the funding. **Describe the role** of any sponsors or funders in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. If the funders had **no role** in any of the above, include this sentence at the end of your statement: "*The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*" However, if the study was **unfunded**, please provide a statement that clearly indicates this, for example: "*The author(s) received no specific funding for this work.*" * typeset	Data acquisition and analyses were funded by AstraZeneca. This was a collaborative study. Employees of the sponsor were part of the study steering committee and participated in the study design. All authors, including those employed by AstraZeneca, participated in the data interpretation, decision to publish, and preparation of the manuscript.
Competing Interests You are responsible for recognizing and disclosing on behalf of all authors any competing interest that could be perceived to bias their work, acknowledging all financial support and any other relevant financial or non-financial competing interests. Do any authors of this manuscript have competing interests (as described in the PLOS Policy on Declaration and Evaluation of Competing Interests)?	I have read the journal's policy and the authors of this manuscript have the following competing interests: MK is an employee of the Observational and Pragmatic Research Institute Pte LTD, which conducted this study and which has conducted paid research in respiratory disease on behalf of the following other organizations in the past 5 years: Aerocrine; AKL Ltd.; Almirall; AstraZeneca; British Lung Foundation; Boehringer Ingelheim; Chiesi; GlaxoSmithKline; Mylan; Mundipharma; Napp; Novartis; Orion; Respiratory Effectiveness Group; Takeda; Teva; and Zentiva, a Sanofi company. JN is an employee, and TNT, GG, and SR are employees and shareholders of AstraZeneca, which supplied the funding for this study. MvdB has, within the last 5 years, received research grants paid to the University of Groningen from AstraZeneca, GlaxoSmithKline, Teva, and Chiesi. GB has, within the last 5 years, received honoraria for lectures from AstraZeneca, Boehringer-Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Pfizer, and Teva; he is a member of advisory boards for AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Novartis, Sanofi/Regeneron, and Teva. RJ reports grants, personal fees and non-financial support from Astra Zeneca,

If yes, please provide details about any and all competing interests in the box below. Your response should begin with this statement: *I have read the journal's policy and the authors of this manuscript have the following competing interests:* **If no** authors have any competing interests to declare, please enter this statement in the box: "*The authors have declared that no competing interests exist.*" * typeset	personal fees from Boehringer Ingelheim, personal fees from Chiesi, personal fees and non-financial support from GSK, grants and personal fees from Novartis, non-financial support from Nutricia, personal fees from Pfizer, outside the submitted work. JWHK reports grants and personal fees from AstraZeneca, grants and personal fees from Boehringer Ingelheim, grants from Chiesi, grants and personal fees from GSK, grants and personal fees from Novartis, grants from Mundi Pharma, grants from TEVA, outside the submitted work. AMG has attended advisory boards for Glaxo SmithKline, Novartis, AstraZeneca, Boehringer Ingelheim andTeva. He has received speaker fees from Novartis, AstraZeneca, Vectura, Boehringer Ingelheim and Teva. He has participated in research with Hoffman La Roche, GlaxoSmithKline and Boehringer Ingelheim. He has attended international conferences sponsored by AstraZeneca and Boehringer Ingelheim. He has consultancy agreements with AstraZeneca and Vectura. IDP has received speaker's honoraria for speaking at sponsored meetings from AstraZeneca, Boehringer Inglehiem, Aerocrine, Almirall, Novartis, and GSK and a payment for organising an educational event for SPRs from AZ. He has received honoraria for attending advisory panels with Almirall, Genentech, Regeneron, AstraZeneca, Boehringer Ingelheim, GSK, MSD, Schering-Plough, Novartis, Dey, Napp and Respivert. He has received sponsorship to attend international scientific meetings from Boehringer Ingelheim, GSK, AstraZeneca and Napp. DBP has board membership with Aerocrine, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Mundipharma, Napp, Novartis, and Teva Pharmaceuticals; consultancy agreements with Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mylan, Mundipharma, Napp, Novartis, Pfizer, Teva Pharmaceuticals, and Theravance; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from Aerocrine, AKL Research and Development Ltd, AstraZeneca, Boehringer Ingelheim, British Lung Foundation, Chiesi, Mylan, Mundipharma, Napp, Novartis, Pfizer, Respiratory Effectiveness Group, Teva Pharmaceuticals, Theravance, UK National Health Service, Zentiva; payment for lectures/speaking engagements from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Mylan, Merck, Mundipharma, Novartis, Pfizer, Skyepharma, and Teva Pharmaceuticals; payment for manuscript preparation from Mundipharma and Teva Pharmaceuticals; payment for the development of educational materials from Mundipharma and Novartis; payment for travel/accommodation/meeting expenses from Aerocrine, AstraZeneca, Boehringer Ingelheim, Mundipharma, Napp, Novartis, and Teva Pharmaceuticals; funding for patient enrolment or completion of research from Chiesi, Novartis, Teva Pharmaceuticals, and Zentiva; stock/stock options from AKL Research and Development Ltd which produces phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care Ltd (Australia and UK) and 74% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); and is peer reviewer for grant committees of the Efficacy and Mechanism Evaluation programme, and Health Technology Assessment.
Ethics Statement You must provide an ethics statement if your study involved human participants, specimens or tissue samples, or vertebrate animals, embryos or tissues. All information entered here should **also be included in the Methods section** of your manuscript. Please write "N/A" if your study does not require an ethics statement. **Human Subject Research (involved**	The study was performed in compliance with all applicable local and international laws and regulations and to standards suggested for observational studies. The study protocol was approved by the CPRD Independent Scientific Advisory Committee (ISAC approval number 16_236) and registered with the European Union electronic Register of Post-Authorisation Studies (EU PAS Register number EUPAS15869). No patient identifying information was accessible during the study.

human participants and/or tissue) All research involving human participants must have been approved by the authors' Institutional Review Board (IRB) or an equivalent committee, and all clinical investigation must have been conducted according to the principles expressed in the Declaration of Helsinki. Informed consent, written or oral, should also have been obtained from the participants. If no consent was given, the reason must be explained (e.g. the data were analyzed anonymously) and reported. The form of consent (written/oral), or reason for lack of consent, should be indicated in the Methods section of your manuscript. Please enter the name of the IRB or Ethics Committee that approved this study in the space below. Include the approval number and/or a statement indicating approval of this research. **Animal Research (involved vertebrate animals, embryos or tissues)** All animal work must have been conducted according to relevant national and international guidelines. If your study involved non-human primates, you must provide details regarding animal welfare and steps taken to ameliorate suffering; this is in accordance with the recommendations of the Weatherall report, "The use of non-human primates in research." The relevant guidelines followed and the committee that approved the study should be identified in the ethics statement. If anesthesia, euthanasia or any kind of animal sacrifice is part of the study, please include briefly in your statement which substances and/or methods were applied. Please enter the name of your Institutional Animal Care and Use Committee (IACUC) or other relevant ethics board, and indicate whether they approved this research or granted a formal waiver of ethical approval. Also include an approval number if one was obtained.	

Field Permit Please indicate the name of the institution or the relevant body that granted permission.	
Data Availability PLOS journals require authors to make all data underlying the findings described in their manuscript fully available, without restriction and from the time of publication, with only rare exceptions to address legal and ethical concerns (see the PLOS Data Policy and FAQ for further details). When submitting a manuscript, authors must provide a Data Availability Statement that describes where the data underlying their manuscript can be found. Your answers to the following constitute your statement about data availability and will be included with the article in the event of publication. **Please note that simply stating 'data available on request from the author' is not acceptable.** ***If, however, your data are only available upon request from the author(s), you must answer "No" to the first question below, and explain your exceptional situation in the text box provided.*** Do the authors confirm that all data underlying the findings described in their manuscript are fully available without restriction?	No - some restrictions will apply
Please describe where your data may be found, writing in full sentences. **Your answers should be entered into the box below and will be published in the form you provide them, if your manuscript is accepted.** If you are copying our sample text below, please ensure you replace any instances of XXX with the appropriate details. If your data are all contained within the paper and/or Supporting Information files, please state this in your answer below. For example, "All relevant data are within the paper and its Supporting Information files." If your data are held or will be held in a public repository, include URLs, accession numbers or DOIs. For example, "All XXX files are available from the XXX database (accession number(s) XXX, XXX)." If this information will only be available after acceptance, please	The dataset supporting the conclusions of this article was derived from the Clinical Practice Datalink (CPRD; http://www.cprd.com) and linked Hospital Episode Statistics (http://content.digital.nhs.uk/hes). The study protocol was approved by the CPRD Independent Scientific Advisory Committee (ISAC approval number 16_236). We do not have permission to give public access to these datasets; however, researchers may request access for their own purposes.

indicate this by ticking the box below. If neither of these applies but you are able to provide details of access elsewhere, with or without limitations, please do so in the box below. For example: “Data are available from the XXX Institutional Data Access / Ethics Committee for researchers who meet the criteria for access to confidential data.” “Data are from the XXX study whose authors may be contacted at XXX.” * typeset	
Additional data availability information:	

RE: PONE-D-18-12337

Stelios Loukides
Academic Editor

Dear Dr. Loukides:

Thank you for the review of our manuscript and for giving us the opportunity to provide a revision.

As instructed, we have resubmitted the following items, each as a separate file:

- A rebuttal letter that responds to each point raised by you and the reviewers, labeled 'Response to Reviewers'
- A marked-up copy of our manuscript that highlights changes made to the original version, labeled 'Revised Manuscript with Track Changes'
- An unmarked version of our revised paper without tracked changes, labeled 'Manuscript'

In addition, we have ensured that our revised manuscript meets *PLOS ONE*'s style requirements, including those for file naming.

Finally, as requested, we have included further details below on sharing the de-identified data set and an updated Funding Statement. The updated Competing Interests Statement follows my signature. Thank you for changing the online submission form on our behalf.

Data sharing restrictions
The dataset supporting the conclusions of this article was derived from the Clinical Practice Datalink (CPRD; http://www.cprd.com) and linked Hospital Episode Statistics (http://content.digital.nhs.uk/hes). The study protocol was approved by the CPRD Independent Scientific Advisory Committee (ISAC approval number 16_236). We do not have permission to give public access to these datasets; however, researchers may request access for their own purposes.

Funding Statement
Data acquisition and analyses were funded by AstraZeneca. This was a collaborative study involving both employees of the sponsor and an independent steering committee. The funder of the study participated in the study design, decision to publish, and preparation of the manuscript. In addition, the funder provided support in the form of salaries for authors TNT, GG, JN, and SR. Employees of the sponsor were part of the study steering committee and participated in the study design. All authors, including those employed by AstraZeneca, participated in the data interpretation, decision to publish, and preparation of the manuscript. All authors had full access to study results and had final responsibility for the decision to submit for publication. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

Yours sincerely,

David Price, for the authors

Prof David B. Price, FRCGP
Observational & Pragmatic Research Institute Pte Ltd, Singapore, Singapore
Academic Primary Care, University of Aberdeen, Aberdeen, UK; Email: dprice@opri.sg

Competing Interests Statement
I have read the journal's policy and the authors of this manuscript have the following competing interests:

MK is an employee of the Observational and Pragmatic Research Institute Pte Ltd, which conducted this study and which has conducted paid research in respiratory disease on behalf of the following other organizations in the past 5 years: Aerocrine; AKL Ltd.; Almirall; AstraZeneca; British Lung Foundation; Boehringer Ingelheim; Chiesi; GlaxoSmithKline; Mylan; Mundipharma; Napp; Novartis; Orion; Respiratory Effectiveness Group; Takeda; Teva; and Zentiva, a Sanofi company.

JN is an employee, and TNT, GG, and SR are employees and shareholders of AstraZeneca, which supplied the funding for this study.

MvdB has, within the last 5 years, received research grants paid to the University of Groningen from AstraZeneca, GlaxoSmithKline, Teva, and Chiesi.

GB has, within the last 5 years, received honoraria for lectures from AstraZeneca, Boehringer-Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Pfizer, and Teva; he is a member of advisory boards for AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Novartis, Sanofi/Regeneron, and Teva.

RJ has received grants from AstraZeneca and GSK, and personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Nutricia and Pfizer outside the submitted work. He was supported by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care South West Peninsula (NIHR CLAHRC South West Peninsula).

JWHK reports grants and personal fees from AstraZeneca, grants and personal fees from Boehringer Ingelheim, grants from Chiesi, grants and personal fees from GSK, grants and personal fees from Novartis, grants from Mundi Pharma, grants from TEVA, outside the submitted work.

AMG has attended advisory boards for Glaxo SmithKline, Novartis, AstraZeneca, Boehringer Ingelheim andTeva. He has received speaker fees from Novartis, AstraZeneca, Vectura, Boehringer Ingelheim and Teva. He has participated in research with Hoffman La Roche, GlaxoSmithKline and Boehringer Ingelheim. He has attended international conferences sponsored by AstraZeneca and Boehringer Ingelheim. He has consultancy agreements with AstraZeneca and Vectura.

IDP has received speaker’s honoraria for speaking at sponsored meetings from AstraZeneca, Boehringer Inglehiem, Aerocrine, Almirall, Novartis, and GSK and a payment for organising an educational event for SPRs from AZ. He has received honoraria for attending advisory panels with Almirall, Genentech, Regeneron, AstraZeneca, Boehringer Ingelheim, GSK, MSD, Schering-Plough, Novartis, Dey, Napp and Respivert. He has received sponsorship to attend international scientific meetings from Boehringer Ingelheim, GSK, AstraZeneca and Napp.

DBP has board membership with Aerocrine, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Mundipharma, Napp, Novartis, and Teva Pharmaceuticals; consultancy agreements with Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mylan, Mundipharma, Napp, Novartis, Pfizer, Teva Pharmaceuticals, and Theravance; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and

Pragmatic Research Institute Pte Ltd) from Aerocrine, AKL Research and Development Ltd, AstraZeneca, Boehringer Ingelheim, British Lung Foundation, Chiesi, Mylan, Mundipharma, Napp, Novartis, Pfizer, Respiratory Effectiveness Group, Teva Pharmaceuticals, Theravance, UK National Health Service, Zentiva; payment for lectures/speaking engagements from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Mylan, Merck, Mundipharma, Novartis, Pfizer, Skyepharma, and Teva Pharmaceuticals; payment for manuscript preparation from Mundipharma and Teva Pharmaceuticals; payment for the development of educational materials from Mundipharma and Novartis; payment for travel/accommodation/meeting expenses from Aerocrine, AstraZeneca, Boehringer Ingelheim, Mundipharma, Napp, Novartis, and Teva Pharmaceuticals; funding for patient enrolment or completion of research from Chiesi, Novartis, Teva Pharmaceuticals, and Zentiva; stock/stock options from AKL Research and Development Ltd which produces phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care Ltd (Australia and UK) and 74% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); and is peer reviewer for grant committees of the Efficacy and Mechanism Evaluation programme, and Health Technology Assessment.

Association between blood eosinophil count and risk of readmission for patients with asthma: historical cohort study

Short title: Blood eosinophil count and risk of readmission for asthma

Marjan Kerkhof[1], Trung N. Tran[2], Maarten van den Berge[3], Guy G. Brusselle[4], Gokul Gopalan[2], Rupert C. M. Jones[5], Janwillem W. H. Kocks[3], Andrew Menzies-Gow[6], Javier Nuevo[7], Ian D. Pavord[8], Sarang Rastogi[2], David B. Price[1,9*]

1 Observational & Pragmatic Research Institute Pte Ltd, Singapore, Singapore

2 AstraZeneca, Gaithersburg, MD, USA

3 University of Groningen, University Medical Center Groningen, Groningen, Netherlands

4 Ghent University Hospital, Ghent, Belgium

5 The Peninsula College of Medicine and Dentistry, Plymouth, UK

6 Royal Brompton and Harefield NHS Foundation Trust, London, UK

7 AstraZeneca, Madrid, Spain

8 Respiratory Medicine Unit and Oxford Respiratory NIHR BRC, Nuffield Department of Medicine, University of Oxford, Oxford, UK

9 Academic Primary Care, University of Aberdeen, Aberdeen, UK

* Corresponding author

Email: dprice@opri.sg (DBP)

Abstract

Background

Recent studies have demonstrated an association between high blood eosinophil counts and greater risk of asthma exacerbations. We sought to determine whether patients hospitalized for an asthma exacerbation were at greater risk of readmission if they had a high blood eosinophil count documented before the first hospitalization.

Methods

This historical cohort study drew on 2 years of medical record data (Clinical Practice Research Datalink with Hospital Episode Statistics linkage) of patients (aged ≥5 years) admitted to hospital in England for asthma, with recorded blood eosinophil count within 1 baseline year before admission. We analyzed the association between high blood eosinophil count ($\geq 0.35 \times 10^9$ cells/L) and readmission risk during 1 year of follow-up after hospital discharge, with adjustment for predefined, relevant confounders using forward selection.

Results

We identified 2,613 eligible patients with asthma-related admission, of median age 51 years (interquartile range, 36-69) and 76% women (1,997/2,613). Overall, 835/2,613 (32.0%) had a preadmission high blood eosinophil count. During the follow-up year, 130/2,613 patients (5.0%) were readmitted for asthma, including 55/835 (6.6%) with vs. 75/1,778 (4.2%) without high blood eosinophil count at baseline (adjusted hazard ratio [HR] 1.49; 95% CI 1.04-2.13, p=0.029). The association was strongest in never-smokers (n=1,296; HR 2.16, 95% CI 1.27-3.68, p=0.005) and absent in current smokers (n=547; HR 1.00, 95% CI 0.49-2.04, p=0.997).

Conclusions

A high blood eosinophil count in the year before an asthma-related hospitalization is associated with increased risk of readmission within the following year. These findings suggest that patients with asthma and preadmission high blood eosinophil count require careful follow-up, with treatment optimization, after discharge.

Key words: asthma; eosinophils; patient readmission

Introduction

Severe asthma exacerbations may result in hospital admissions, relatively rare but important events with adverse implications for patients' quality of life, health care resource use, and related costs. Approximately 83,000 hospital episodes (including inpatient, day-case, and intensive care episodes) were recorded as related to asthma in England in 2011-2012, representing approximately 3.3 million patients with clinician-reported, diagnosed-and-treated asthma in England during that time [1].

Recent studies have demonstrated an association between high blood eosinophil counts and greater risk of asthma exacerbations, especially in patients with asthma that is not well-controlled [2,3]. Moreover, among patients with severe asthma in a US cohort study, the odds of asthma-related hospital admissions were significantly greater for patients with high blood eosinophil count defined as $\geq 0.4 \times 10^9$ cells/L than for those with counts of $< 0.4 \times 10^9$ cells/L [4]. Similarly, in the UK, patients with severe uncontrolled eosinophilic asthma (blood eosinophil count $\geq 0.3 \times 10^9$ cells/L) experienced over 7 times the number of hospitalizations per year compared with the general asthma population [5], and in Finland, a blood eosinophil count $> 0.3 \times 10^9$ cells/L was associated with 13% greater rate of hospital admissions (vs. $\leq 0.3 \times 10^9$ cells/L) among patients with asthma [6]. Targeted therapy for patients with severe eosinophilic asthma can reduce the rate of exacerbations requiring hospitalization and/or an emergency department (ED) visit [7,8].

Patients who are admitted to hospital for asthma-related reasons, such as a severe exacerbation, may be at risk of short-term readmission to hospital. For example, some patients with persistent airways inflammation are at risk of readmission after discharge despite treatment with corticosteroids [9,10]. Predictors of readmission are important to identify as this

information could be used to improve in-hospital and post-hospitalization patient management to minimize subsequent readmissions. Several demographic and socioeconomic risk factors for hospital readmissions have been reported for patients with asthma, including older age, greater number of comorbidities, an urban hospital setting, and longer length of hospital stay [11,12]. A recent study found that elevated blood eosinophil count ($\geq 0.3 \times 10^9$ cells/L) in the first blood sample upon hospitalization was associated with a lower incidence of hospital readmissions as compared with an eosinophil count $<0.3 \times 10^9$ cells/L [13]. Conversely, for patients with chronic obstructive pulmonary disease (COPD), a recent publication reports an association of increased readmissions with blood eosinophil count $\geq 0.20 \times 10^9$ cells/L at first hospitalization [14]. The variability in associations may be because blood eosinophils are prognostic and theragnostic.

The aim of this study was to determine if patients hospitalized for an asthma exacerbation were more likely to be readmitted if their preadmission blood eosinophil count was elevated. Our hypothesis was that standard management of asthma exacerbations is insufficient to prevent readmissions for patients who have high blood eosinophil counts in the year preceding a hospitalization.

Methods

Data source

We used primary and secondary care data from the Clinical Practice Research Datalink (CPRD) and linked Hospital Episode Statistics (HES) for this historical cohort study of patients with asthma who had been admitted to hospital in England. The CPRD is a large well-validated database, frequently used for medical and health research, that contains de-identified, longitudinal medical records of 5 million patients from >600 UK practices [15]. The linked HES

data include detailed information about hospital admissions, ED visits, and outpatient visits to secondary care in England [16]. We used the HES Admitted Patient Care database, which contains records of patients who were admitted to a hospital ward, including patients who visited an ED before admission and those who were admitted to an intensive care unit. Diagnostic and treatment data are recorded in the CPRD using Read codes, while diagnosis data are recorded in HES using International Classification of Disease (ICD)-10 clinical coding and OPCS4 procedural coding.

The study dataset spanned the period from April 1997 through February 2016.

Study design and patients

Eligible patients were 5 years or older at the time of their most recent asthma diagnosis and had active asthma, which we defined as (1) a diagnostic Read code for asthma qualifying for inclusion in the asthma registry, which general practices in the UK maintain for the Quality Outcomes Framework (QOF) [17], (2) no recorded asthma-resolved Read code after the last asthma diagnosis code, and (3) at least 2 prescriptions for asthma (controller or reliever medication) during 1 baseline year. Patients admitted to hospital with asthma as the primary diagnosis (ICD-10 code J45-J46) were eligible for the study if they had one or more valid blood eosinophil counts recorded during the year before the hospital admission with no prescription for oral corticosteroids within 2 weeks before the eosinophil count.

Eligible patients had to have available, continuous data throughout the study period (Fig 1), which included ≥1 baseline year before discharge from the hospital for patient characterization and ≥1 outcome year after hospital discharge for follow-up (except for patients who died within 1 year after hospital discharge). We included the first hospitalization recorded

for each patient meeting those criteria. A diagnostic Read code for any of the following chronic respiratory conditions recorded at any time was cause for exclusion from the study: bronchiectasis, pulmonary sarcoidosis, hypersensitivity pneumonitis, malignancy of the lungs, interstitial lung disease, and cystic fibrosis. Patients with concomitant diagnosis of COPD were not excluded.

Fig 1. Study Design.

The study was performed in compliance with all applicable local and international laws and regulations and to standards suggested for observational studies, including an independent advisory group, use of an *a priori* analysis plan, and study registration with commitment to publish [18]. The study protocol was approved by the CPRD Independent Scientific Advisory Committee (ISAC approval number 16_236) and registered with the European Union electronic Register of Post-Authorisation Studies (EU PAS Register number EUPAS15869) [19]. No patient identifying information was accessible during the study.

Outcome assessments

The exposure of interest was the most recent blood eosinophil count measured within 1 year before hospital admission. For patients who had multiple tests in the baseline year, we used the blood eosinophil count (with no oral corticosteroid prescription within 2 weeks prior) that was closest to the admission. A high blood eosinophil count was defined as $\geq 0.35 \times 10^9$ cells/L (or $\geq 0.4 \times 10^9$ cells/L when counts were recorded to only 1 decimal place). This value was chosen based on our findings in a prior study in which patients with blood eosinophil counts $>0.3 \times 10^9$ cells/L experienced more severe exacerbations and poorer asthma control [3].

The primary outcome was readmission to hospital with asthma as primary diagnosis (ICD-10 code J45/J46) over a 4-week outcome period and over a 1-year outcome period after discharge from the hospital (Fig 1). The secondary outcome was readmission to hospital with asthma as a secondary/subsidiary diagnosis and a respiratory condition as primary diagnosis (ICD-10 codes J00-J99), again observed over 4 weeks and 1 year.

Statistical analysis

Patients' baseline characteristics and hospital readmissions were compared between patients with high and normal blood eosinophil counts using Pearson's χ^2 test of independent categories for categorical variables, and the Mann-Whitney test for continuous variables.

Kaplan-Meier curves were constructed for patients with and without high blood eosinophil count for the maximum follow-up period of 1 year after hospital discharge. Comparisons were made with log-rank analyses, and patients were censored if they died.

Cox proportional hazard regression, with the time from hospital discharge date to the first readmission date as the "survival" time, was performed to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for the association between high blood eosinophil count and time to readmission, adjusted for potential confounders. The following variables were evaluated for their potential confounding effect on the effect estimate: sex, age, body mass index (BMI), smoking habits, timing of blood eosinophil count relative to the first hospitalization, Charlson comorbidity index (categorical as 0, 1−4, ≥5), comorbidities, and Global Initiative for Asthma [20] (GINA) treatment step (S1 Table). The likelihood of a blood eosinophil count being recorded was greater at dates closer to the hospital admission, and we included the time between recorded eosinophil count and first hospitalization as a confounder in the Cox regression model. Final models were

arrived at following a forward-selection procedure, in which variables were added one-by-one and retained if the coefficient for the effect estimate (high eosinophil count) changed by ≥5%. Co-linearity was checked by evaluating variance inflation factors, which were all under 5%. The validity of the proportional hazards assumption was checked by examination of survival curves, and p-values were calculated using a Wald test.

Potential effect modification of smoking status was tested for significance by including an interaction term into the full model. We conducted several sensitivity analyses, repeating the outcome analyses using alternative definitions of high blood eosinophil counts ($\geq 0.25 \times 10^9$ cells/L or $\geq 0.3 \times 10^9$ cells/L if rounded, and $\geq 0.45 \times 10^9$ cells/L or $\geq 0.5 \times 10^9$ cells/L if rounded) and examining outcomes in two subsets of patients: (1) after exclusion of those who initiated inhaled corticosteroids (ICS) after their first asthma-related hospital admission and (2) after exclusion of patients with a concomitant diagnosis of COPD.

Statistical analyses were conducted using IBM SPSS Statistics version 23 (IBM SPSS Statistics, Feltham, Middlesex, UK) and R version 3.0.2 (The R Project for Statistical Computing; https://www.r-project.org/). A statistically significant result was defined as $p \leq 0.05$.

Results

Patients

Of 146,485 patients in the CPRD with HES data linkage, 22,940 (16%) patients had at least one hospital admission for asthma and ≥2 years of medical record data, and 3,611 patients (16%) of those hospitalized had an eosinophil count recorded within 1 year before the hospitalization (and no oral corticosteroid prescription within 2 weeks prior). Of these 3,611

patients, 2,613 patients (72%) were ≥5 years old, had active asthma, and were eligible for the study (Fig 2).

Fig 2. Flow Diagram Showing Selection of Eligible Patients from the Database.

CPRD = Clinical Practice Research Database. HES = Hospital Episode Statistics. OCS = oral corticosteroid. QOF = Quality Outcomes Framework.

In the study population, 482 of 2,613 patients (18%) were discharged from hospital on the same day. Six patients died (one patient died 31 weeks after readmission for asthma and was not censored; others were censored) during 1 year of follow up.

Characteristics of the total population with blood eosinophil count (n=2,613) and 13,016 patients with asthma who met all eligibility criteria except availability of blood eosinophil count during baseline are presented in S2 Table. There were multiple statistically significant differences between the two groups of patients. Eligible patients with recorded eosinophil count were older than the 13,016 patients without eosinophil count (median age, 50 vs. 33 years), more commonly female (1,997/2,613, 76% vs. 7,542/13,016, 58%), heavier (mean BMI 29.1 vs. 26.0 kg/m^2), and receiving a higher median ICS dose (219 vs. 132 µg/day, fluticasone-propionate equivalent) during the baseline year (S2 Table).

A high blood eosinophil count ($\geq 0.35 \times 10^9$ cells/L) was recorded during the year before the hospital admission for 835 of 2,613 patients (32%). The high blood eosinophil cohort had a median age of 45 (vs. 54 years in the cohort with eosinophil count of $<0.35 \times 10^9$ cells/L) and included proportionately fewer women and fewer overweight and obese patients (Table 1). In addition, patients with eosinophil count $\geq 0.35 \times 10^9$ cells/L were more likely to be never-smokers and to have a recorded diagnosis of rhinitis, atopic eczema, or nasal polyps.

213

214

215 **Table 1. Baseline Demographic and Clinical Characteristics.**

Variable	All patients (N = 2,613)	Blood eosinophil cohort		P value[a]
		<0.35x10^9 cells/L (n = 1,778)	≥0.35x10^9 cells/L (n = 835)	
Age				
Median (IQR)	51.0 (36.0-69.0)	54.0 (39.0-70.3)	45.0 (30.0-65.0)	<0.0001
5-12 years	56 (2.1)	17 (1.0)	39 (4.7)	<0.0001
13-17 years	77 (2.9)	31 (1.7)	46 (5.5)	
18-64 years	1,681 (64.3)	1,141 (64.2)	540 (64.7)	
≥65 years	799 (30.6)	589 (33.1)	210 (25.1)	
Female sex	1,997 (75.7)	1,392 (78.3)	585 (70.1)	<0.0001
Smoking status[b]				
Data available	2,597 (99.4)	1,771 (99.6)	826 (98.9)	
Current smoker	547 (21.1)	378 (21.3)	169 (20.5)	0.007
Ex-smoker	754 (29.0)	544 (30.7)	210 (25.4)	
Never smoker	1,296 (49.9)	849 (47.9)	447 (54.1)	
Body mass index[b]				
Data available	2,260 (86.5)	1,551 (87.2)	709 (84.9)	
Mean (SD)	29.2 (7.0)	29.6 (7.0)	28.4 (7.0)	<0.0001
<18.5 kg/m^2	78 (3.5)	38 (2.5)	40 (5.6)	<0.0001
≥18.5 kg/m^2 to <25 kg/m^2	625 (27.7)	393 (25.3)	232 (32.7)	
≥25 kg/m^2 to <30 kg/m^2	625 (27.7)	450 (29.0)	175 (24.7)	
≥30 kg/m^2	932 (41.2)	670 (43.2)	262 (37.0)	
Allergic/non-allergic rhinitis[c]	876 (33.5)	545 (30.7)	331 (39.6)	<0.0001
Atopic eczema[c]	927 (35.5)	595 (33.5)	332 (39.8)	<0.0001
Nasal polyps[c]	83 (3.2)	39 (2.2)	44 (5.3)	<0.0001
Chronic rhinosinusitis[c]	579 (22.2)	400 (22.5)	179 (21.4)	0.54
COPD[c]	284 (10.9)	192 (10.8)	92 (11.0)	0.87
GERD[c]	474 (18.1)	355 (20.0)	119 (14.3)	<0.001
Cardiovascular disease[c]	654 (25.0)	491 (27.6)	163 (19.5)	<0.0001
Charlson comorbidity index				
0	611 (23.4)	429 (24.1)	182 (21.8)	0.028
1-4	1,661 (63.6)	1,101 (61.9)	560 (67.1)	
≥5	341 (13.1)	248 (13.9)	93 (11.1)	
GINA step of asthma treatment[b]				
1	124 (4.7)	78 (4.4)	46 (5.5)	0.009
2	493 (18.9)	357 (20.1)	136 (16.3)	
3	468 (17.9)	298 (16.8)	170 (20.4)	
4	1,220 (46.7)	848 (47.7)	372 (44.6)	
5	308 (11.8)	197 (11.1)	111 (13.3)	
≥1 ICS inhaler prescribed	2,444 (93.5)	1,671 (94.0)	773 (92.6)	0.173

Daily dose of ICS (µg/day), median (IQR)[d]	262 (110-521)	263 (110-534)	247 (99-492)	0.041
≥1 SABA inhaler prescribed	2,432 (93.1)	1,646 (92.6)	786 (94.1)	0.144
Daily SABA dose, median (IQR)[d]	1.64 (0.82-3.55)	1.64 (0.66-3.29)	2.04 (0.82-4.11)	<0.0001
OCS daily dose (g), median (IQR)	0.55 (0-1.64)	0.55 (0-1.56)	0.55 (0-1.75)	0.139
No. severe asthma exacerbations				
0	747 (28.6)	516 (29.0)	231 (27.7)	0.25
1	848 (32.5)	589 (33.1)	259 (31.0)	
2	506 (19.4)	345 (19.4)	161 (19.3)	
3	266 (10.2)	174 (9.8)	92 (11.0)	
≥4	246 (9.4)	154 (8.7)	92 (11.0)	

Data expressed as No. (%) unless otherwise noted. COPD = chronic obstructive pulmonary disease. GERD = gastroesophageal reflux disease. GINA = Global Initiative for Asthma; ICS = inhaled corticosteroid; OCS = oral corticosteroid; SABA = short-acting β-agonist.

[a]P-value comparing blood eosinophil cohorts, computed from χ^2 test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the p-value is from the Mann-Whitney test.

[b]The closest BMI within 10 years of hospital discharge, and the smoking status closest to and within 5 years before hospital discharge, were included. The GINA treatment step was determined based on the last prescription before the hospitalization (S1 Table). The BMI categories applied to patients ≥18 years old; for children, BMI was not calculated because accurate information on age in months required to calculate BMI z-scores was not provided for privacy reasons.

[c]Comorbidities were those with diagnostic Read code ever-recorded in the available data before hospital discharge.

[d]ICS dose expressed as fluticasone propionate equivalent (µg/day), and one SABA dose defined as 200 µg in albuterol equivalents.

The likelihood of a blood eosinophil count being recorded was greater at dates closer to the hospital admission (S1 Fig). Patients with measurements within 4 weeks before the hospitalization were more likely to have a high blood eosinophil count (128/339, 38%) than those with measurement within a longer time period before the hospitalization (707/2274, 31%; p=0.014). The length of time between recorded eosinophil count and admission with asthma as the primary diagnosis was greater in patients with high blood eosinophil counts than in patients without high counts, but the difference in distribution was not statistically significant (144 days [IQR, 56−250] vs. 131 days [58−229], p=0.159).

The median duration of hospitalization (2 nights) was the same in patients with and without a high blood eosinophil count; however, there were fewer patients with a high blood eosinophil count who had a long hospital stay (Table 2).

Table 2. Duration of Hospitalization.

Variable	All patients (N = 2,613)	Blood eosinophil cohort		P value[a]
		<0.35x10^9 cells/L (n = 1,778)	≥0.35x10^9 cells/L (n = 835)	
Nights in hospital, median (IQR)		2 (1–5)	2 (1–4)	
No. nights in hospital, n (%)				
0	482 (18.4)	323 (18.2)	159 (19.0)	0.006
1	529 (20.2)	349 (19.6)	180 (21.6)	
2	356 (13.6)	230 (12.9)	126 (15.1)	
3	281 (10.8)	182 (10.2)	99 (11.9)	
4	243 (9.3)	162 (9.1)	81 (9.7)	
5	149 (5.7)	99 (5.6)	50 (6.0)	
6	142 (5.4)	106 (6.0)	36 (4.3)	
≥7	431 (16.5)	327 (18.4)	104 (12.5)	

[a]P-value comparing blood eosinophil cohorts computed from χ^2 test.

Readmissions by eosinophil cohort

Only 6 patients were readmitted to the hospital within 4 weeks of the first admission, with no significant difference between blood eosinophil cohorts (Table 3). At 1 year, 130 of 2,613 (5%) patients overall were readmitted for asthma, including a significantly greater percentage of patients with high vs. normal blood eosinophil count (Table 3; Fig 3). Patients with eosinophil count of ≥0.35x10^9 cells/L had a 49% higher adjusted risk of readmission to hospital for asthma in the first year of follow-up than patients without a high count (HR 1.49; 95% CI 1.04–2.13; p=0.029; Table 3).

Table 3. Readmissions to Hospital within 4 Weeks and 1 Year and Hazard Ratios for Readmission in the High Eosinophil Count Cohort.

Readmission	Eosinophil cohort: $<0.35x10^9$ cells/L (n = 1,778)	Eosinophil cohort: $\geq 0.35x10^9$ cells/L (n = 835)	P value[a]	Adjusted HR (95% CI) for blood eosinophil count $\geq 0.35x10^9/L$[b]	P value
With asthma as primary diagnosis (n = 2,613)					
Within 4 weeks	4 (0.2)	2 (0.2)	0.94	--	--
Within 1 year	75 (4.2)	55 (6.6)	0.009	1.49 (1.04-2.13)	0.029
By known smoking status (n = 2,597)[c]					
Never-smokers (n = 1,296)	29 (3.4)	30 (6.7)	0.007	2.16 (1.27-3.68)	0.005
Ex-smokers (n = 754)	19 (3.5)	13 (6.2)	0.010	1.49 (0.73-3.06)	0.27
Current smokers (n = 547)	27 (7.1)	12 (7.1)	0.99	1.00 (0.49-2.04)	0.997
Never/ex-smokers pooled (n = 2,050)	48 (3.4)	43 (6.5)	0.002	1.78 (1.17-2.73)	0.007
With respiratory condition other than asthma, and asthma as subsidiary diagnosis (n = 2,613)					
Within 4 weeks	22 (1.2)	8 (1.0)	0.53	--	--
Within 1 year	81 (4.6)	39 (4.7)	0.90	1.12 (0.76-1.65)	0.57

[a]P-value computed using χ^2 test.

[b]Adjusted for sex, age, smoking status, timing of blood eosinophil count measurement, duration of index hospitalization.

[c]16 patients with no recent record of smoking status were excluded from the analyses by smoking status.

Fig 3. Kaplan-Meier Curves Describing the Cumulative "Survival" of a Readmission to Hospital for Asthma in the First Year After an Admission with Asthma as the Primary Diagnosis in Patients With and Without High Blood Eosinophil Count.

Interaction with smoking status

The effect of current smoking was non-significant (p=0.073) when tested by including an interaction term for current smoking (yes/no) and high blood eosinophil count (yes/no) into the model. The increased readmission rate with a high blood eosinophil count was found only in non-smokers (HR 1.84; 1.20–2.80; p=0.005) and not in current smokers (HR 0.88; 0.44–1.76; p=0.73). In this analysis of all 2,613 patients, 16 patients without recent, recorded smoking status were included as non-smokers (never-smokers plus ex-smokers).

Results were similar for patients with known smoking status, with a significant 216% higher adjusted risk of readmission for never-smokers with high blood eosinophil count, and no additional risk for current smokers with high blood eosinophil count (Table 3). Although the association was most pronounced in never-smokers, no significant difference in the association was found between never-smokers and ex-smokers (p=0.67) in the 2,050 patients recorded as not currently smoking.

Sensitivity analyses

A high blood eosinophil count was recorded for 1,328 patients (51%) when defined as $\geq 0.25 \times 10^9$ cells/L, and for 588 patients (23%) when defined as $\geq 0.45 \times 10^9$ cells/L. The association between a high blood eosinophil count and readmission to hospital for asthma was less pronounced and not significant for patients with blood eosinophil count of either $\geq 0.25 \times 10^9$ cells/L (HR=1.17; 0.82−1.66; p=0.39) or $\geq 0.45 \times 10^9$ cells/L (HR=1.15; 0.77−1.72; p=0.50; S3 Table). The association was also not significant in never-smokers or in never/ex-smokers combined using either definition of high blood eosinophil count (S3 Table).

A total of 169 of the 2,613 patients (6%) had no prescription for ICS in the baseline year before being hospitalized for asthma; of the 169, 115 (68%) had ICS prescribed in the outcome

year. After exclusion of these 115 patients, HRs for the association with blood eosinophil count of $\geq 0.35 \times 10^9$ cells/L slightly increased as compared with those for the full population (S3 Table). The HR was 1.77 (95% CI, 1.15−2.72; p=0.009) for never/ex-smokers combined, which was very similar to the HR for never/ex-smokers combined of the full population (1.78). However, effect modification by current smokers was not significant in this subpopulation (p=0.28).

Results of an additional subanalysis excluding patients with a concomitant diagnosis of COPD showed no relevant difference in association for the remaining 2,329 patients (HR= 1.48; 95% CI 1.01–2.17, p=0.045; see S3 Table).

Discussion

In this large, historical cohort study, we found that patients who had a blood eosinophil count of $\geq 0.35 \times 10^9$ cells/L recorded in the year preceding an asthma-related hospitalization had a significantly greater risk of readmission for asthma during the year after they were discharged. Few patients (n=6) were readmitted to hospital for asthma within 4 weeks after discharge, while by 1 year after discharge, 5% (130 of 2,613) patients were readmitted for asthma. The greater risk of readmission during 1 year follow-up was present only for patients with high blood eosinophil count who were never- or ex-smokers (not for current smokers).

Our study is one of few studies examining hospital readmissions for asthma in a general asthma population and in the real-life setting. Readmissions in the present study were comparatively infrequent relative to results in other studies: for example, in one US study, approximately 4% of patients were readmitted for an asthma exacerbation within 30 days [21], and in France from 2002–2005, 15% were readmitted for asthma within 1 year [22]. The overall

rate of hospital admissions for asthma in England appears to be lower that than for Western Europe as a whole, the latter reported in 2004 to be 7% [1,23].

Other recent studies of hospital readmissions have been limited to patients on systemic corticosteroids [9], have examined readmissions up to only 30 days [11,12,24], were much smaller [24], and/or were conducted at a single institution [25,26]. None of these studies, nor others examining readmissions after 30 days [27-29], examined the association of hospital readmissions with blood eosinophil count. While Gonzalez-Barcala et al. [13] in their retrospective study at a single hospital in Spain found differently from the present study that elevated eosinophil count was associated with a lower incidence of readmissions, it is difficult to compare their study with ours because of differences in methods. For example, the reference blood eosinophil count was that taken upon admission rather than before hospitalization during a baseline year, and the length of the follow-up period for analyzing readmissions is unclear [13].

An interesting finding in the present study that requires further investigation is the effect of smoking status on association of readmissions with eosinophil count. Cigarette smoking increases levels of oxidative stress, alters airway immune responses, and increases risk of hospitalization in patients with asthma [30]. Westerhof et al. [31] in their study of patients with severe asthma found that frequent exacerbations were associated with blood eosinophil count only in never smokers and not in ex-smokers, for whom blood neutrophil count was an independent predictor of frequent exacerbations (smokers not studied). In our study, both never- and ex-smokers (but not current smokers) who had a high eosinophil count were at greater risk of asthma-related readmission, although for ex-smokers separately this association was not statistically significant. Moreover, in our study the difference in association between non-smokers (never-plus ex-smokers pooled) and smokers was large and statistically significant.

Clearly, additional work is needed to examine biomarker and peripheral blood cell profiles in relation to smoking status and hospital readmissions and other asthma-related outcomes.

The median duration of hospitalization (2 nights) was the same in both normal and high blood eosinophil cohorts; however, patients with a high blood eosinophil count were less likely to have a hospital stay longer than 5 nights (17% vs. 24% of those without high eosinophil count). This finding illustrates the conundrum of eosinophilic asthma: while it tends to be more severe in terms of exacerbations and asthma control, eosinophilic asthma is also potentially more responsive to therapies targeting type 2 inflammation, including ICS and biologics.

We speculated that the association between eosinophil count and readmission could be diluted for patients with eosinophil count performed several months before the first admission; therefore, we re-examined outcomes including only patients with eosinophil counts measured close to the initial hospitalization to see if the association were stronger. However, when selecting those with eosinophil count recorded within 4 months before hospitalization, the numbers became small and associations non-significant, although the direction of the effect was the same: for never- and ex-smokers pooled (n=915), the risk of readmission was 51% greater but non-significant (adjusted HR 1.69;0.60–4.76; p=0.32).

A strength of this study is that we included a broad patient population with asthma, not limited to those with severe asthma. We selected inclusion criteria to ensure that patients' asthma was actively managed in advance of the hospital admission, thereby excluding patients experiencing a first episode of asthma diagnosed at the time of admission. Moreover, we required that patients had not received an oral corticosteroid prescription within 2 weeks before the eosinophil count to obviate the eosinopenic effects of systemic corticosteroids [32,33]. The data sources we used are well-regarded and frequently employed for pharmacoepidemiological

studies [15-17,34]. The primary care data in the CPRD is considered to be high-quality, with recording that has been standardized and improved since the institution in 2004 of the UK Quality Outcomes Framework (QOF) [17], which provides financial incentives for GPs to deliver quality care, including an annual asthma review covering asthma control status, smoking, and inhaler technique. Detailed information about hospital admissions was drawn from HES, a data warehouse linked to the CPRD [16].

Nevertheless, a limitation is that the study dataset comprised information collected for clinical and routine use rather than specifically for research purposes. Moreover, prescriptions for drugs prescribed by specialists are not reliably recorded in the CPRD. Therefore, we could not evaluate treatment prescribed immediately after hospital discharge. However, the daily dose of ICS prescribed by GPs in the year after admission was not significantly different between patients with and without high eosinophil counts (median for both: 329 vs. 329 µg/day fluticasone-equivalent, p=0.70, Mann-Whitney test). Finally, as for all observational studies, there is the possibility of residual confounding from unrecognized and/or unmeasured factors.

A "count-response" association of blood eosinophil levels with risk of asthma exacerbations has been reported in both an observational study [3] and for the placebo arm of clinical trials [35,36]. Our study had insufficient patient numbers to assess the presence of a count-response relationship with hospital readmissions using incremental categories to define high eosinophil count. Our definition of $\geq 0.35 \times 10^9$ cells/L for high blood eosinophil count captured a clear association of high blood eosinophil count with risk of readmission, while there were fewer patients, hence limited statistical power, to evaluate the higher cut-point of $\geq 0.45 \times 10^9$ cells/L, although the direction of the effect was the same. Alternatively, new ICS use or better ICS adherence after the index hospitalization might have reduced the effect of elevated

eosinophil count; however, it would not be easy to quantify this possibility in the framework of a historical cohort study, and in spite of this possibility we found a strong association at the $\geq 0.35 \times 10^9$ cells/L definition.

We did not exclude patients with a concomitant diagnosis of COPD; therefore, approximately one-tenth of the study population appeared to have some form of physician-diagnosed asthma-COPD overlap [37], although these patients were too few to analyze separately. However, the sensitivity analysis excluding these patients supported the findings for the full population.

By necessity we were able to include only patients who had a recorded blood eosinophil count, which is not routinely measured in clinical practice, a factor serving as a possible source of selection bias and thereby limiting the generalizability of our findings. There were large differences in baseline characteristics between the patients with available eosinophil count and those without, who tended to be younger; more likely female, a current smoker, and of normal weight; and less likely having comorbidities such as rhinitis, chronic sinusitis, gastroesophageal reflux disease, and cardiovascular disease. The age differences were expected because older people more frequently have full blood counts available. Further work is needed to examine the use of blood eosinophil count in the clinical assessment of the full spectrum of patients with asthma.

Tailoring asthma therapy using sputum eosinophil counts appears to be effective in reducing exacerbations, particularly for adults with frequent exacerbations [38]. Thus, blood eosinophil count, more practical to measure than sputum eosinophil count, could play a role in tailoring asthma therapy with the goal of reducing exacerbations, hence potentially hospital readmissions. Moreover, further research is needed to identify the mechanism(s) behind the

increased risk of readmission associated with high blood eosinophil count, such as possible undertreatment with ICS or insufficient effectiveness of ICS. In addition, more specifically, a re-examination is needed of the absence of association with readmissions and high blood eosinophil count in current smokers, as there was limited statistical power in this subgroup of patients, reflected by the wide confidence interval.

Conclusions

A high blood eosinophil count in the year before an asthma-related hospitalization is associated with increased risk of readmission within the following year. This risk was slightly greater in the subset of patients who were not new initiators of ICS treatment after their index hospital admission, suggesting that this trait is only partially treatable with anti-inflammatory therapy. This association was present only in non-smoking patients with high blood eosinophil count. Our findings support the benefit of including a full blood count with differential as a routine assessment in clinical practice for patients with not well-controlled asthma. Moreover, our findings support the need for careful follow-up, with treatment optimization, after hospital discharge for patients with asthma and preadmission high blood eosinophil count.

Acknowledgments

Writing and editorial support was provided by Elizabeth V. Hillyer, DVM, supported by the Observational and Pragmatic Research Institute Pte Ltd (OPRI).

References

1. Mukherjee M, Stoddart A, Gupta RP, Nwaru BI, Farr A, Heaven M, et al. The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases. BMC Med. 2016;14:113. doi: 10.1186/s12916-016-0657-8.
2. Zeiger RS, Schatz M, Dalal AA, Chen W, Sadikova E, Suruki RY, et al. Blood eosinophil count and outcomes in severe uncontrolled asthma: a prospective study. J Allergy Clin Immunol Pract. 2017;5:144-53 e8. doi: 10.1016/j.jaip.2016.07.015.
3. Price DB, Rigazio A, Campbell JD, Bleecker ER, Corrigan CJ, Thomas M, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. Lancet Respir Med. 2015;3:849-58. doi: 10.1016/S2213-2600(15)00367-7.
4. Casciano J, Krishnan JA, Small MB, Buck PO, Gopalan G, Li C, et al. Burden of asthma with elevated blood eosinophil levels. BMC Pulm Med. 2016;16:100. doi: 10.1186/s12890-016-0263-8.
5. Kerkhof M, Tran TN, Soriano JB, Golam S, Gibson D, Hillyer EV, et al. Healthcare resource use and costs of severe, uncontrolled eosinophilic asthma in the UK general population. Thorax. 2018;73:116-24. doi: 10.1136/thoraxjnl-2017-210531.
6. Makela MJ, Christensen HN, Karlsson A, Rastogi S, Kettunen K. Health care resource utilization and characteristics of patients with eosinophilic asthma in secondary health care in Finland. Eur Clin Respir J. 2018;5:1458560. doi: 10.1080/20018525.2018.1458560.

7. Yancey SW, Ortega HG, Keene ON, Mayer B, Gunsoy NB, Brightling CE, et al. Meta-analysis of asthma-related hospitalization in mepolizumab studies of severe eosinophilic asthma. J Allergy Clin Immunol. 2017;139:1167-75 e2. doi: 10.1016/j.jaci.2016.08.008.
8. Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. N Engl J Med. 2017;376:2448-58. doi: 10.1056/NEJMoa1703501.
9. Sadatsafavi M, Lynd LD, De Vera MA, Zafari Z, FitzGerald JM. One-year outcomes of inhaled controller therapies added to systemic corticosteroids after asthma-related hospital discharge. Respir Med. 2015;109:320-8. doi: 10.1016/j.rmed.2014.12.014.
10. Suissa S, Ernst P, Kezouh A. Regular use of inhaled corticosteroids and the long term prevention of hospitalisation for asthma. Thorax. 2002;57:880-4.
11. Veeranki SP, Sharma K, Ohabughiro MU, Mehta HB, Adhikari D, Kuo YF, et al. 30-Day readmissions in hospitalized adults with asthma exacerbations: insights from the Nationwide Readmission Database. Chest. 2016;150:1162-5. doi: 10.1016/j.chest.2016.07.043.
12. Veeranki SP, Ohabughiro MU, Moran J, Mehta HB, Ameredes BT, Kuo YF, et al. National estimates of 30-day readmissions among children hospitalized for asthma in the United States. J Asthma. 2017:1-10. doi: 10.1080/02770903.2017.1365888.
13. Gonzalez-Barcala FJ, San-Jose ME, Nieto-Fontarigo JJ, Carreira JM, Calvo-Alvarez U, Cruz MJ, et al. Association between blood eosinophil count with asthma hospital readmissions. Eur J Intern Med. 2018. doi: 10.1016/j.ejim.2018.02.034.

14. Couillard S, Larivee P, Courteau J, Vanasse A. Eosinophils in COPD exacerbations are associated with increased readmissions. Chest. 2017;151:366-73. doi: 10.1016/j.chest.2016.10.003.
15. Clinical Practice Research Datalink. (cited April 16, 2018) Available from: http://www.cprd.com.
16. UK National Health Service. Hospital Episode Statistics (HES). (cited April 16, 2018) Available from: http://content.digital.nhs.uk/hes.
17. UK National Health Service. Quality and Outcomes Framework (QOF). (cited April 16, 2018) Available from: http://www.hscic.gov.uk/qof.
18. Roche N, Reddel H, Martin R, Brusselle G, Papi A, Thomas M, et al. Quality standards for real-world research. Focus on observational database studies of comparative effectiveness. Ann Am Thorac Soc. 2014;11 Suppl 2:S99-S104. doi: 10.1513/AnnalsATS.201309-300RM.
19. The European Union electronic Register of Post-Authorisation Studies (EU PAS Register). (cited April 16, 2018). Available from: http://www.encepp.eu/encepp/studiesDatabase.jsp.
20. Global Initiative for Asthma (GINA). GINA Report, Global Strategy for Asthma Management and Prevention. (cited March 18, 2018). Available from: http://ginasthma.org/.
21. Hasegawa K, Gibo K, Tsugawa Y, Shimada YJ, Camargo CA, Jr. Age-related differences in the rate, timing, and diagnosis of 30-day readmissions in hospitalized adults with asthma exacerbation. Chest. 2016;149:1021-9. doi: 10.1016/j.chest.2015.12.039.

22. Delmas MC, Marguet C, Raherison C, Nicolau J, Fuhrman C. Readmissions for asthma in France in 2002-2005. Rev Mal Respir. 2011;28:e115-22. doi: 10.1016/j.rmr.2011.09.023.

23. Rabe KF, Adachi M, Lai CK, Soriano JB, Vermeire PA, Weiss KB, et al. Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. J Allergy Clin Immunol. 2004;114:40-7.

24. Buyantseva LV, Brooks J, Rossi M, Lehman E, Craig TJ. Risk factors associated with 30-day asthma readmissions. J Asthma. 2016;53:684-90. doi: 10.3109/02770903.2016.1140773.

25. Gonzalez-Barcala FJ, Calvo-Alvarez U, Garcia-Sanz MT, Garcia-Couceiro N, Martin-Lancharro P, Pose A, et al. Asthma exacerbations: risk factors for hospital readmissions. Ir J Med Sci. 2018;187:155-61. doi: 10.1007/s11845-017-1633-9.

26. Pola-Bibian B, Dominguez-Ortega J, Vila-Nadal G, Entrala A, Gonzalez-Cavero L, Barranco P, et al. Asthma exacerbations in a tertiary hospital: clinical features, triggers, and risk factors for hospitalization. J Investig Allergol Clin Immunol. 2017;27:238-45. doi: 10.18176/jiaci.0128.

27. Salamzadeh J, Wong IC, Hosker HS, Chrystyn H. A Cox regression analysis of covariates for asthma hospital readmissions. J Asthma. 2003;40:645-52. doi: 10.1081/JAS-120019035.

28. Sheikh A, Steiner MF, Cezard G, Bansal N, Fischbacher C, Simpson CR, et al. Ethnic variations in asthma hospital admission, readmission and death: a retrospective, national cohort study of 4.62 million people in Scotland. BMC Med. 2016;14:3. doi: 10.1186/s12916-015-0546-6.

29. Beck AF, Huang B, Auger KA, Ryan PH, Chen C, Kahn RS. Explaining racial disparities in child asthma readmission using a causal inference approach. JAMA Pediatr. 2016;170:695-703. doi: 10.1001/jamapediatrics.2016.0269.

30. Polosa R, Thomson NC. Smoking and asthma: dangerous liaisons. Eur Respir J. 2013;41:716-26. doi: 10.1183/09031936.00073312.

31. Westerhof GA, de Groot JC, Amelink M, de Nijs SB, Ten Brinke A, Weersink EJ, et al. Predictors of frequent exacerbations in (ex)smoking and never smoking adults with severe asthma. Respir Med. 2016;118:122-7. doi: 10.1016/j.rmed.2016.08.006.

32. Kellgren JH, Janus O. The eosinopenic response to cortisone and ACTH in normal subjects. Br Med J. 1951;2:1183-7.

33. Fleishaker DL, Mukherjee A, Whaley FS, Daniel S, Zeiher BG. Safety and pharmacodynamic dose response of short-term prednisone in healthy adult subjects: a dose ranging, randomized, placebo-controlled, crossover study. BMC Musculoskelet Disord. 2016;17:293. doi: 10.1186/s12891-016-1135-3.

34. Boston Collaborative Drug Surveillance Program. The Clinical Practice Research Datalink. (cited April 16, 2018). Available from: http://www.bu.edu/bcdsp/gprd/.

35. Ortega HG, Yancey SW, Mayer B, Gunsoy NB, Keene ON, Bleecker ER, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. Lancet Respir Med. 2016;4:549-56. doi: 10.1016/S2213-2600(16)30031-5.

36. FitzGerald JM, Bleecker ER, Menzies-Gow A, Zangrilli JG, Hirsch I, Metcalfe P, et al. Predictors of enhanced response with benralizumab for patients with severe asthma:

pooled analysis of the SIROCCO and CALIMA studies. Lancet Respir Med. 2018;6:51-64. doi: 10.1016/S2213-2600(17)30344-2.

37. van den Berge M, Aalbers R. The asthma-COPD overlap syndrome: how is it defined and what are its clinical implications? J Asthma Allergy. 2016;9:27-35. doi: 10.2147/JAA.S78900.

38. Petsky HL, Li A, Chang AB. Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults. Cochrane Database Syst Rev. 2017;8:CD005603. doi: 10.1002/14651858.CD005603.pub3.

Supporting information

S1 Table. Definitions Applied for Global Initiative for Asthma (GINA) Treatment Step, Determined Using Each Patient's Last Prescription(s) Before the First Hospital Admission.

S2 Table. Demographic and Clinical Characteristics of All Eligible Patients with Blood Eosinophil Count and of Patients Meeting All Eligibility Criteria Except Availability of Eosinophil Count.[a]

S1 Fig. Distribution of the Number of Days before Hospital Discharge on Which the Most Recent Eosinophil Measurement Was Recorded.

S3 Table. Readmissions for Asthma within 1 Year and Hazard Ratios for Readmission in the High Eosinophil Count Cohort: Sensitivity Analyses.

Figure 1

Click here to download Figure Fig1.tif

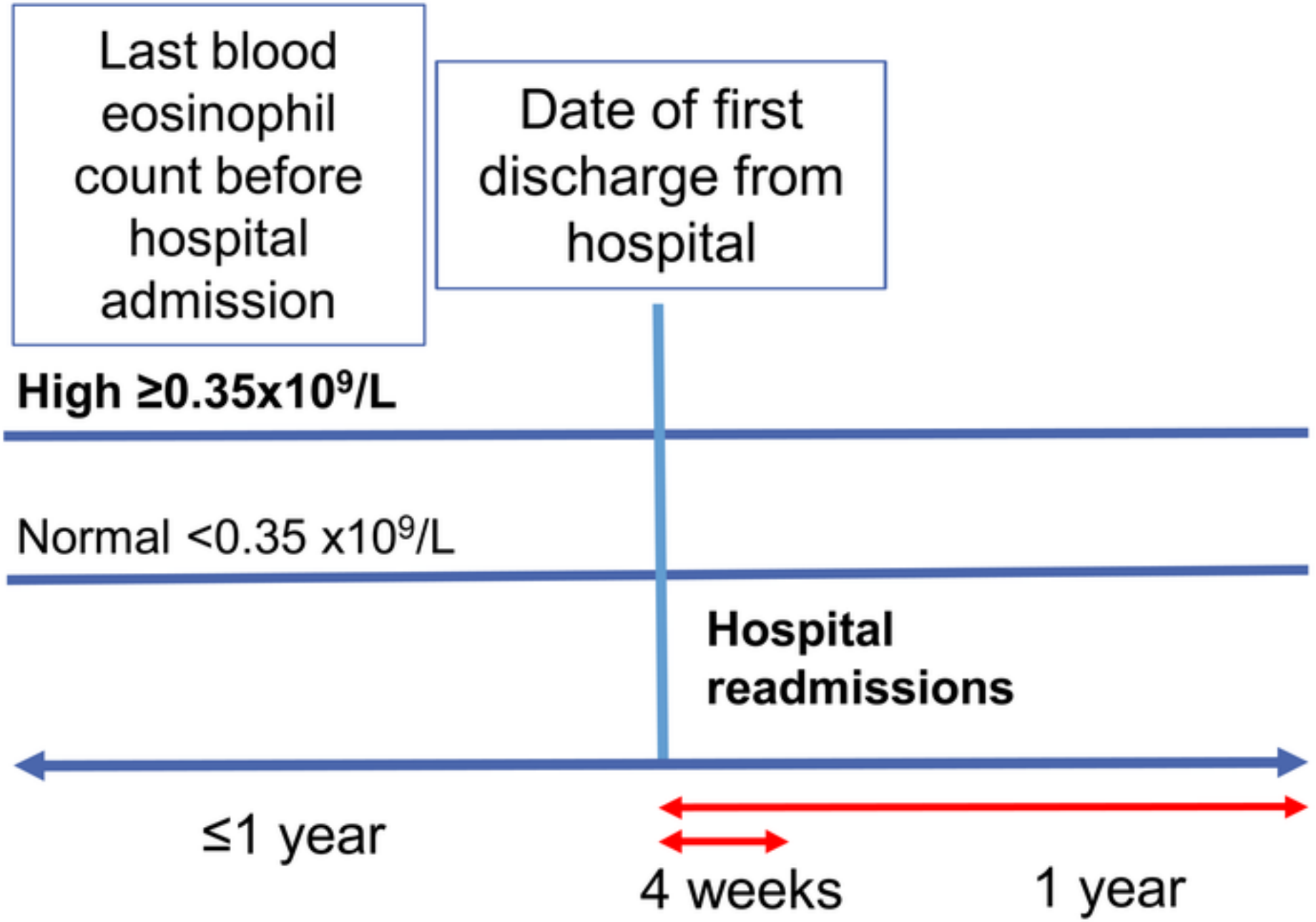


Figure 2

Click here to download Figure Fig2.tif

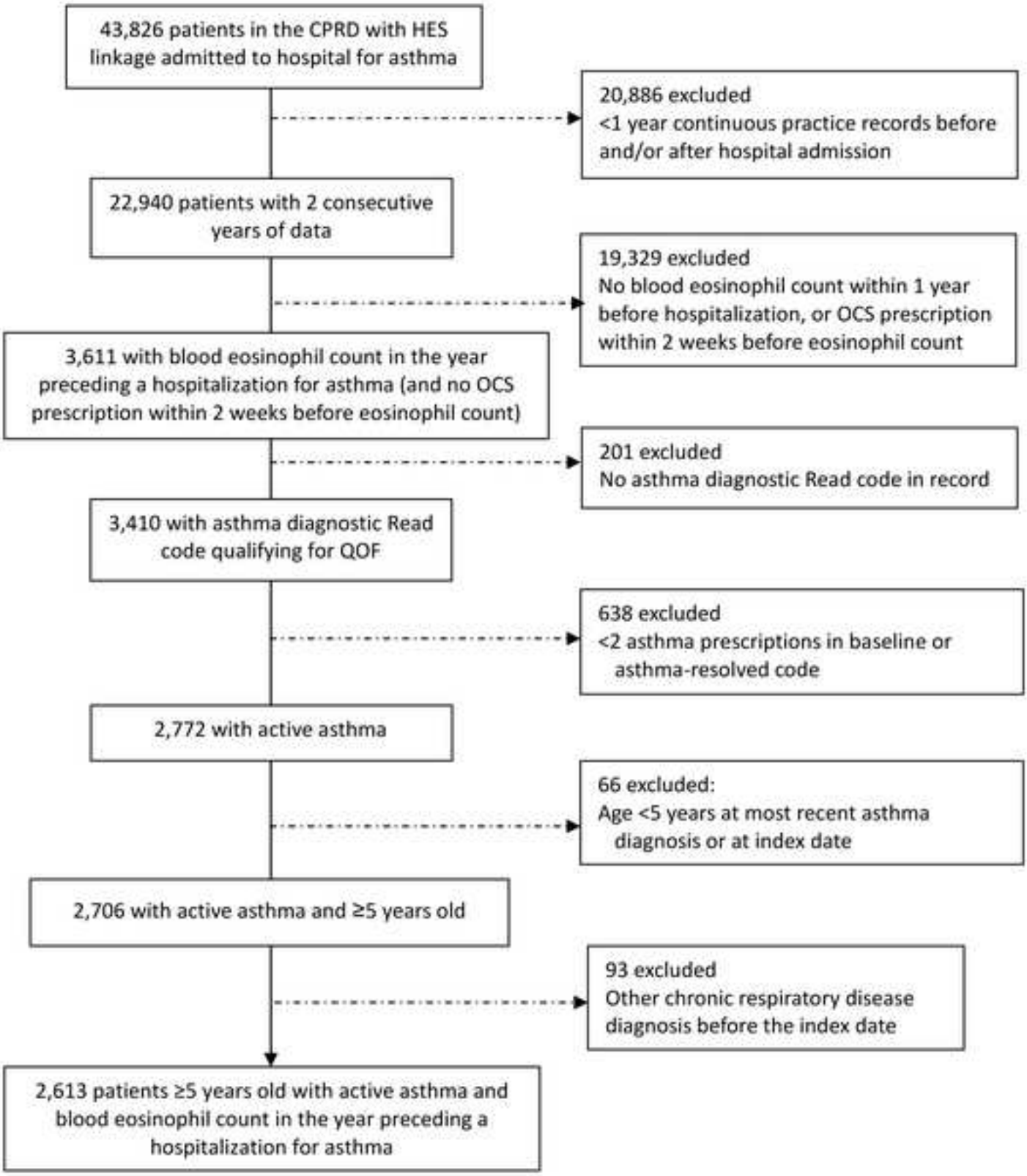
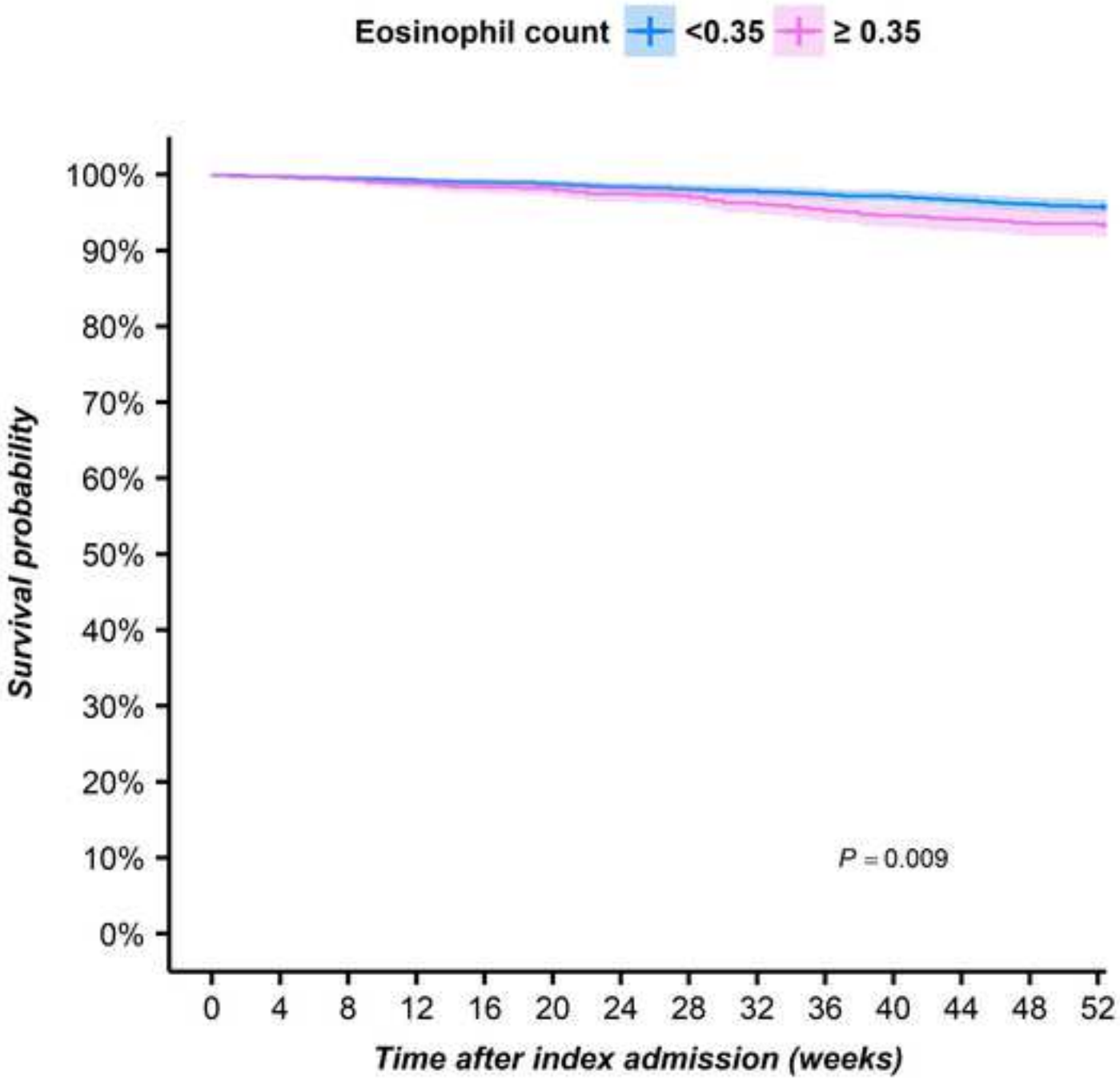


Figure 3

Click here to download Figure Fig3.tif



S1 Table

S1 Figure

Click here to access/download

Supporting Information

S1 Fig-1.tif

Association between blood eosinophil count and risk of readmission for patients with asthma: historical cohort study

Short title: Blood eosinophil count and risk of readmission for asthma

Marjan Kerkhof[1], Trung N. Tran[2], Maarten van den Berge[3], Guy G. Brusselle[4], Gokul Gopalan[2], Rupert C. M. Jones[5], Janwillem W. H. Kocks[3], Andrew Menzies-Gow[6], Javier Nuevo[7], Ian D. Pavord[8], Sarang Rastogi[2], David B. Price[1,9*]

1 Observational & Pragmatic Research Institute Pte Ltd, Singapore, Singapore

2 AstraZeneca, Gaithersburg, MD, USA

3 University of Groningen, University Medical Center Groningen, Groningen, Netherlands

4 Ghent University Hospital, Ghent, Belgium

5 The Peninsula College of Medicine and Dentistry, Plymouth, UK

6 Royal Brompton and Harefield NHS Foundation Trust, London, UK

7 AstraZeneca, Madrid, Spain

8 Respiratory Medicine Unit and Oxford Respiratory NIHR BRC, Nuffield Department of Medicine, University of Oxford, Oxford, UK

9 Academic Primary Care, University of Aberdeen, Aberdeen, UK

* Corresponding author

Email: dprice@opri.sg (DBP)

Abstract

Background

Recent studies have demonstrated an association between high blood eosinophil counts and greater risk of asthma exacerbations. We sought to determine whether patients hospitalized for an asthma exacerbation were at greater risk of readmission if they had a high blood eosinophil count documented before the first hospitalization.

Methods

This historical cohort study drew on 2 years of medical record data (Clinical Practice Research Datalink with Hospital Episode Statistics linkage) of patients (aged ≥5 years) admitted to hospital in England for asthma, with recorded blood eosinophil count within 1 baseline year before admission. We analyzed the association between high blood eosinophil count (≥$0.35x10^9$ cells/L) and readmission risk during 1 year of follow-up after hospital discharge, with adjustment for predefined, relevant confounders using forward selection.

Results

We identified 2,613 eligible patients with asthma-related admission, of median age 51 years (interquartile range, 36-69) and 76% women (1,997/2,613). Overall, 835/2,613 (32.0%) had a preadmission high blood eosinophil count. During the follow-up year, 130/2,613 patients (5.0%) were readmitted for asthma, including 55/835 (6.6%) with vs. 75/1,778 (4.2%) without high blood eosinophil count at baseline (adjusted hazard ratio [HR] ~~1.45~~1.49; 95% CI 1.~~02~~04-2.~~08~~13, p=0.~~040~~029). The association was strongest in never-smokers (n=1,296; HR ~~1.95~~2.16, 95% CI ~~1.16~~1.27-~~3.31~~3.68, p=0.~~013~~005) and absent in current smokers (n=547; HR ~~0.97~~1.00, 95% CI 0.~~48~~49-~~1.97~~2.04, p=0.~~94~~997).

Conclusions

A high blood eosinophil count in the year before an asthma-related hospitalization is associated with increased risk of readmission within the following year. These findings suggest that patients with asthma and preadmission high blood eosinophil count require careful follow-up, with treatment optimization, after discharge.

Key words: asthma; eosinophils; patient readmission

Introduction

Severe asthma exacerbations may result in hospital admissions, relatively rare but important events with adverse implications for patients' quality of life, health care resource use, and related costs. Approximately 83,000 hospital episodes (including inpatient, day-case, and intensive care episodes) were recorded as related to asthma in England in 2011-2012, representing approximately 3.3 million patients with clinician-reported, diagnosed-and-treated asthma in England during that time [1].

Recent studies have demonstrated an association between high blood eosinophil counts and greater risk of asthma exacerbations, especially in patients with asthma that is not well-controlled [2,3]. Moreover, among patients with severe asthma in a US cohort study, the odds of asthma-related hospital admissions were significantly greater for patients with high blood eosinophil count defined as $\geq 0.4 \times 10^9$ cells/L than for those with counts of $< 0.4 \times 10^9$ cells/L [4]. Similarly, in the UK, patients with severe uncontrolled eosinophilic asthma (blood eosinophil count $\geq 0.3 \times 10^9$ cells/L) experienced over 7 times the number of hospitalizations per year compared with the general asthma population [5], and in Finland, a blood eosinophil count $> 0.3 \times 10^9$ cells/L was associated with 13% greater rate of hospital admissions (vs. $\leq 0.3 \times 10^9$ cells/L) among patients with asthma [6]. Targeted therapy for patients with severe eosinophilic asthma can reduce the rate of exacerbations requiring hospitalization and/or an emergency department (ED) visit [~~6,7~~7,8].

Patients who are admitted to hospital for asthma-related reasons, such as a severe exacerbation, may be at risk of short-term readmission to hospital. For example, some patients with persistent airways inflammation are at risk of readmission after discharge despite treatment with corticosteroids [~~8,9~~9,10]. Predictors of readmission are important to identify as this

information could be used to improve in-hospital and post-hospitalization patient management to minimize subsequent readmissions. ~~While s~~Several demographic and socioeconomic risk factors for hospital readmissions have been reported for patients with asthma, including older age, greater number of comorbidities, an urban hospital setting, and longer length of hospital stay [~~10,11~~11,12]. A recent study found that~~, the association between~~ elevated blood eosinophil count ~~and~~ ($\geq$0.3x10^9 cells/L) in the first blood sample upon hospitalization was associated with a lower incidence of hospital readmissions as compared with an eosinophil count <0.3x10^9 cells/L [13].~~has not been examined for a general asthma population. For~~ Conversely, for patients with chronic obstructive pulmonary disease (COPD), a recent publication reports an association of increased readmissions with blood eosinophil count $\geq$0.20x10^9 cells/L at first hospitalization [~~12~~14]. The variability in associations may be because blood eosinophils are prognostic and theragnostic.

The aim of this study was to determine if patients hospitalized for an asthma exacerbation were more likely to be readmitted if their preadmission blood eosinophil count was elevated. Our hypothesis was that standard management of asthma exacerbations is insufficient to prevent readmissions for patients who have high blood eosinophil counts in the year preceding a hospitalization.

Methods

Data source

We used primary and secondary care data from the Clinical Practice Research Datalink (CPRD) and linked Hospital Episode Statistics (HES) for this historical cohort study of patients with asthma who had been admitted to hospital in England. The CPRD is a large well-validated

database, frequently used for medical and health research, that contains de-identified, longitudinal medical records of 5 million patients from >600 UK practices [~~13~~15]. The linked HES data include detailed information about hospital admissions, ED visits, and outpatient visits to secondary care in England [~~14~~16]. We used the HES Admitted Patient Care database, which contains records of patients who were admitted to a hospital ward, including patients who visited an ED before admission and those who were admitted to an intensive care unit. Diagnostic and treatment data are recorded in the CPRD using Read codes, while diagnosis data are recorded in HES using International Classification of Disease (ICD)-10 clinical coding and OPCS4 procedural coding.

The study dataset spanned the period from April 1997 through February 2016.

Study design and patients

Eligible patients were 5 years or older at the time of their most recent asthma diagnosis and had active asthma, which we defined as (1) a diagnostic Read code for asthma qualifying for inclusion in the asthma registry, which general practices in the UK maintain for the Quality Outcomes Framework (QOF) [~~15~~17], (2) no recorded asthma-resolved Read code after the last asthma diagnosis code, and (3) at least 2 prescriptions for asthma (controller or reliever medication) during 1 baseline year. Patients admitted to hospital with asthma as the primary diagnosis (ICD-10 code J45-J46) were eligible for the study if they had one or more valid blood eosinophil counts recorded during the year before the hospital admission with no prescription for oral corticosteroids within 2 weeks before the eosinophil count.

Eligible patients had to have available, continuous data throughout the study period (Fig 1), which included ≥1 baseline year before discharge from the hospital for patient

characterization and ≥1 outcome year after hospital discharge for follow-up (except for patients who died within 1 year after hospital discharge). We included the first hospitalization recorded for each patient meeting those criteria. A diagnostic Read code for any of the following chronic respiratory conditions recorded at any time was cause for exclusion from the study: bronchiectasis, pulmonary sarcoidosis, hypersensitivity pneumonitis, malignancy of the lungs, interstitial lung disease, and cystic fibrosis. Patients with concomitant diagnosis of COPD were not excluded.

Fig 1. Study Design.

The study was performed in compliance with all applicable local and international laws and regulations and to standards suggested for observational studies, including an independent advisory group, use of an *a priori* analysis plan, and study registration with commitment to publish [~~16~~18]. The study protocol was approved by the CPRD Independent Scientific Advisory Committee (ISAC approval number 16_236) and registered with the European Union electronic Register of Post-Authorisation Studies (EU PAS Register number EUPAS15869) [~~17~~19]. No patient identifying information was accessible during the study.

Outcome assessments

The exposure of interest was the most recent blood eosinophil count measured within 1 year before hospital admission. For patients who had multiple tests in the baseline year, we used the blood eosinophil count (with no oral corticosteroid prescription within 2 weeks prior) that was closest to the admission. A high blood eosinophil count was defined as $\geq 0.35 \times 10^9$ cells/L (or $\geq 0.4 \times 10^9$ cells/L when counts were recorded to only 1 decimal place). This value was chosen

based on our findings in a prior study in which patients with blood eosinophil counts >$0.3x10^9$ cells/L experienced more severe exacerbations and poorer asthma control [3].

The primary outcome was readmission to hospital with asthma as primary diagnosis (ICD-10 code J45/J46) over a 4-week outcome period and over a 1-year outcome period after discharge from the hospital (Fig 1). The secondary outcome was readmission to hospital with asthma as a secondary/subsidiary diagnosis and a respiratory condition as primary diagnosis (ICD-10 codes J00-J99), again observed over 4 weeks and 1 year.

Statistical analysis

Patients' baseline characteristics and hospital readmissions were compared between patients with high and normal blood eosinophil counts using Pearson's χ^2 test of independent categories for categorical variables, and the Mann-Whitney test for continuous variables.

Kaplan-Meier curves were constructed for patients with and without high blood eosinophil count for the maximum follow-up period of 1 year after hospital discharge. Comparisons were made with log-rank analyses, and patients were censored if they died.

Cox proportional hazard regression, with the time from hospital discharge date to the first readmission date as the "survival" time, was performed to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for the association between high blood eosinophil count and time to readmission, adjusted for potential confounders. The following variables were evaluated for their potential confounding effect on the effect estimate: sex, age, body mass index (BMI), smoking habits, timing of blood eosinophil count relative to the first hospitalization, Charlson comorbidity index (categorical as 0, 1−4, ≥5), comorbidities, and Global Initiative for Asthma [~~18~~20] (GINA) treatment step (S1 Table). The likelihood of a blood eosinophil count being recorded was greater

at dates closer to the hospital admission, and we included the time between recorded eosinophil count and first hospitalization as a confounder in the Cox regression model. Final models were arrived at following a forward-selection procedure, in which variables were added one-by-one and retained if the coefficient for the effect estimate (high eosinophil count) changed by ≥5%. Co-linearity was checked by evaluating variance inflation factors, which were all under 5%. The validity of the proportional hazards assumption was checked by examination of survival curves, and p-values were calculated using a Wald test.

Potential effect modification of smoking status was tested for significance by including an interaction term into the full model. We conducted ~~two~~ several sensitivity analyses, repeating the outcome analyses using alternative definitions of high blood eosinophil counts ($\geq 0.25 \times 10^9$ cells/L or $\geq 0.3 \times 10^9$ cells/L if rounded, and $\geq 0.45 \times 10^9$ cells/L or $\geq 0.5 \times 10^9$ cells/L if rounded) and examining outcomes in ~~a~~ two subsets of patients: (1) after exclusion of those who initiated inhaled corticosteroids (ICS) after their first asthma-related hospital admission and (2) after exclusion of patients with a concomitant diagnosis of COPD.

Statistical analyses were conducted using IBM SPSS Statistics version 23 (IBM SPSS Statistics, Feltham, Middlesex, UK) and R version 3.0.2 (The R Project for Statistical Computing; https://www.r-project.org/). A statistically significant result was defined as $p \leq 0.05$.

Results

Patients

Of 146,485 patients in the CPRD with HES data linkage, 22,940 (16%) patients had at least one hospital admission for asthma and ≥2 years of medical record data, and 3,611 patients (16%) of those hospitalized had an eosinophil count recorded within 1 year before the

hospitalization (and no oral corticosteroid prescription within 2 weeks prior). Of these 3,611 patients, 2,613 patients (72%) were ≥5 years old, had active asthma, and were eligible for the study (Fig 2).

Fig 2. Flow Diagram Showing Selection of Eligible Patients from the Database.

CPRD = Clinical Practice Research Database. HES = Hospital Episode Statistics. OCS = oral corticosteroid. QOF = Quality Outcomes Framework.

In the study population, 482 of 2,613 patients (18%) were discharged from hospital on the same day. Six patients died (one patient died 31 weeks after readmission for asthma and was not censored; others were censored) during 1 year of follow up.

Characteristics of the total population with blood eosinophil count (n=2,613) and ~~23,731~~13,016 patients with asthma who met all eligibility criteria except availability of blood eosinophil count during baseline are presented in S2 Table. There were multiple statistically significant differences between the two groups of patients. Eligible patients with recorded eosinophil count were older than the ~~23,731~~13,016 patients without eosinophil count (median age, ~~51~~ 50 vs. ~~31~~ 33 years), more commonly female (1,997/2,613, 76% vs. ~~14,337/23,731~~7,542/13,016, ~~60%~~58%), heavier (mean BMI ~~29.2~~29.1 vs. ~~26.5~~26.0 kg/m^2), and receiving a higher median ICS dose (~~262~~ 219 vs. ~~164~~ 132 µg/day, fluticasone-propionate equivalent) during the baseline year (S2 Table).

A high blood eosinophil count (≥0.35x10^9 cells/L) was recorded during the year before the hospital admission for 835 of 2,613 patients (32%). The high blood eosinophil cohort had a median age of 45 (vs. 54 years in the cohort with eosinophil count of <0.35x10^9 cells/L) and included proportionately fewer women and fewer overweight and obese patients (Table 1). In

addition, patients with eosinophil count $\geq 0.35 \times 10^9$ cells/L were more likely to be never-smokers and to have a recorded diagnosis of rhinitis, atopic eczema, or nasal polyps.

219 **Table 1. Baseline Demographic and Clinical Characteristics.**

Variable	All patients (N = 2,613)	Blood eosinophil cohort		P value[a]
		<0.35x10^9 cells/L (n = 1,778)	≥0.35x10^9 cells/L (n = 835)	
Age				
Median (IQR)	51.0 (36.0-69.0)	54.0 (39.0-70.3)	45.0 (30.0-65.0)	<0.0001
5-12 years	56 (2.1)	17 (1.0)	39 (4.7)	<0.0001
13-17 years	77 (2.9)	31 (1.7)	46 (5.5)	
18-64 years	1,681 (64.3)	1,141 (64.2)	540 (64.7)	
≥65 years	799 (30.6)	589 (33.1)	210 (25.1)	
Female sex	1,997 (75.7)	1,392 (78.3)	585 (70.1)	<0.0001
Smoking status[b]				
Data available	2,597 (99.4)	1,771 (99.6)	826 (98.9)	
Current smoker	547 (21.1)	378 (21.3)	169 (20.5)	0.007
Ex-smoker	754 (29.0)	544 (30.7)	210 (25.4)	
Never smoker	1,296 (49.9)	849 (47.9)	447 (54.1)	
Body mass index[b]				
Data available	2,260 (86.5)	1,551 (87.2)	709 (84.9)	
Mean (SD)	29.2 (7.0)	29.6 (7.0)	28.4 (7.0)	<0.0001
<18.5 kg/m^2	78 (3.5)	38 (2.5)	40 (5.6)	<0.0001
≥18.5 kg/m^2 to <25 kg/m^2	625 (27.7)	393 (25.3)	232 (32.7)	
≥25 kg/m^2 to <30 kg/m^2	625 (27.7)	450 (29.0)	175 (24.7)	
≥30 kg/m^2	932 (41.2)	670 (43.2)	262 (37.0)	
Allergic/non-allergic rhinitis[c]	876 (33.5)	545 (30.7)	331 (39.6)	<0.0001
Atopic eczema[c]	927 (35.5)	595 (33.5)	332 (39.8)	<0.0001
Nasal polyps[c]	83 (3.2)	39 (2.2)	44 (5.3)	<0.0001
Chronic rhinosinusitis[c]	579 (22.2)	400 (22.5)	179 (21.4)	0.54
COPD[c]	284 (10.9)	192 (10.8)	92 (11.0)	0.87
GERD[c]	474 (18.1)	355 (20.0)	119 (14.3)	<0.001
Cardiovascular disease[c]	654 (25.0)	491 (27.6)	163 (19.5)	<0.0001
Charlson comorbidity index				
0	611 (23.4)	429 (24.1)	182 (21.8)	0.028
1-4	1,661 (63.6)	1,101 (61.9)	560 (67.1)	
≥5	341 (13.1)	248 (13.9)	93 (11.1)	
GINA step of asthma treatment[b]				
1	124 (4.7)	78 (4.4)	46 (5.5)	0.009
2	493 (18.9)	357 (20.1)	136 (16.3)	
3	468 (17.9)	298 (16.8)	170 (20.4)	
4	1,220 (46.7)	848 (47.7)	372 (44.6)	
5	308 (11.8)	197 (11.1)	111 (13.3)	
≥1 ICS inhaler prescribed	2,444 (93.5)	1,671 (94.0)	773 (92.6)	0.173

Daily dose of ICS (µg/day), median (IQR)[d]	262 (110-521)	263 (110-534)	247 (99-492)	0.041
≥1 SABA inhaler prescribed	2,432 (93.1)	1,646 (92.6)	786 (94.1)	0.144
Daily SABA dose, median (IQR)[d]	1.64 (0.82-3.55)	1.64 (0.66-3.29)	2.04 (0.82-4.11)	<0.0001
OCS daily dose (g), median (IQR)	0.55 (0-1.64)	0.55 (0-1.56)	0.55 (0-1.75)	0.139
No. severe asthma exacerbations				
0	747 (28.6)	516 (29.0)	231 (27.7)	0.25
1	848 (32.5)	589 (33.1)	259 (31.0)	
2	506 (19.4)	345 (19.4)	161 (19.3)	
3	266 (10.2)	174 (9.8)	92 (11.0)	
≥4	246 (9.4)	154 (8.7)	92 (11.0)	

Data expressed as No. (%) unless otherwise noted. COPD = chronic obstructive pulmonary disease. GERD = gastroesophageal reflux disease. GINA = Global Initiative for Asthma; ICS = inhaled corticosteroid; OCS = oral corticosteroid; SABA = short-acting β-agonist.

[a]P-value comparing blood eosinophil cohorts, computed from χ^2 test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the p-value is from the Mann-Whitney test.

[b]The closest BMI within 10 years of hospital discharge, and the smoking status closest to and within 5 years before hospital discharge, were included. The GINA treatment step was determined based on the last prescription before the hospitalization (S1 Table). The BMI categories applied to patients ≥18 years old; for children, BMI was not calculated because accurate information on age in months required to calculate BMI z-scores was not provided for privacy reasons.

[c]Comorbidities were those with diagnostic Read code ever-recorded in the available data before hospital discharge.

[d]ICS dose expressed as fluticasone propionate equivalent (µg/day), and one SABA dose defined as 200 µg in albuterol equivalents.

The likelihood of a blood eosinophil count being recorded was greater at dates closer to the hospital admission (S1 Fig). Patients with measurements within 4 weeks before the hospitalization were more likely to have a high blood eosinophil count (128/339, 38%) than those with measurement within a longer time period before the hospitalization (707/2274, 31%; p=0.014). The length of time between recorded eosinophil count and admission with asthma as the primary diagnosis was greater in patients with high blood eosinophil counts than in patients without high counts, but the difference in distribution was not statistically significant (144 days [IQR, 56−250] vs. 131 days [58−229], p=0.159).

The median duration of hospitalization (2 nights) was the same in patients with and without a high blood eosinophil count; however, there were fewer patients with a high blood eosinophil count who had a long hospital stay (Table 2).

Table 2. Duration of Hospitalization.

Variable	All patients (N = 2,613)	Blood eosinophil cohort		P value[a]
		<0.35x10^9 cells/L (n = 1,778)	≥0.35x10^9 cells/L (n = 835)	
Nights in hospital, median (IQR)		2 (1–5)	2 (1–4)	
No. nights in hospital, n (%)				
0	482 (18.4)	323 (18.2)	159 (19.0)	0.006
1	529 (20.2)	349 (19.6)	180 (21.6)	
2	356 (13.6)	230 (12.9)	126 (15.1)	
3	281 (10.8)	182 (10.2)	99 (11.9)	
4	243 (9.3)	162 (9.1)	81 (9.7)	
5	149 (5.7)	99 (5.6)	50 (6.0)	
6	142 (5.4)	106 (6.0)	36 (4.3)	
≥7	431 (16.5)	327 (18.4)	104 (12.5)	

[a]P-value comparing blood eosinophil cohorts computed from χ^2 test.

Readmissions by eosinophil cohort

Only 6 patients were readmitted to the hospital within 4 weeks of the first admission, with no significant difference between blood eosinophil cohorts (Table ~~2~~3). At 1 year, 130 of 2,613 (5%) patients overall were readmitted for asthma, including a significantly greater percentage of patients with high vs. normal blood eosinophil count (Table ~~2~~3; Fig 3). Patients with eosinophil count of ≥0.35x10^9 cells/L had a ~~45%~~49% higher adjusted risk of readmission to hospital for asthma in the first year of follow-up than patients without a high count (HR ~~1.45~~1.49; 95% CI ~~1.02~~1.04–~~2.13~~2.08; p=~~0.040~~0.029; Table ~~2~~3).

Table ~~2~~3. Readmissions to Hospital within 4 Weeks and 1 Year and Hazard Ratios for Readmission in the High Eosinophil Count Cohort.

Readmission	Eosinophil cohort <0.35x10^9 cells/L (n = 1,778)	Eosinophil cohort ≥0.35x10^9 cells/L (n = 835)	P value[a]	Adjusted HR (95% CI) for blood eosinophil count ≥0.35x10^9/L[b]	P value
With asthma as primary diagnosis (n = 2,613)					
Within 4 weeks	4 (0.2)	2 (0.2)	0.94	--	--
Within 1 year	75 (4.2)	55 (6.6)	0.009	1.49 (1.04-2.13)~~1.45 (1.02-2.08)~~	0.029~~0.040~~
By known smoking status (n = 2,597)[c]					
Never-smokers (n = 1,296)	29 (3.4)	30 (6.7)	0.007	2.16 (1.27-3.68)~~1.95 (1.16-3.31)~~	0.005~~0.013~~
Ex-smokers (n = 754)	19 (3.5)	13 (6.2)	0.010	1.49 (0.73-3.06)~~1.52 (0.74-3.10)~~	0.27~~0.25~~
Current smokers (n = 547)	27 (7.1)	12 (7.1)	0.99	1.00 (0.49-2.04)~~0.97 (0.48-1.97)~~	0.997~~0.94~~
Never/ex-smokers pooled (n = 2,050)	48 (3.4)	43 (6.5)	0.002	1.78 (1.17-2.73)~~1.77 (1.16-2.70)~~	0.007~~0.009~~
With respiratory condition other than asthma, and asthma as subsidiary diagnosis (n = 2,613)					
Within 4 weeks	22 (1.2)	8 (1.0)	0.53	~~--~~	~~--~~
Within 1 year	81 (4.6)	39 (4.7)	0.90	1.12 (0.76-1.65)~~1.10 (0.75-1.63)~~	0.57~~0.63~~

[a]P-value computed using χ^2 test.

[b]Adjusted for sex, age, smoking status, timing of blood eosinophil count measurement, duration of index hospitalization.

[c]16 patients with no recent record of smoking status were excluded from the analyses by smoking status.

Fig 3. Kaplan-Meier Curves Describing the Cumulative "Survival" of a Readmission to Hospital for Asthma in the First Year After an Admission with Asthma as the Primary Diagnosis in Patients With and Without High Blood Eosinophil Count.

Interaction with smoking status

~~There was significant~~ The effect ~~modification by~~of current smoking was non-significant (p=~~0.044~~0.073) when tested by including an interaction term for current smoking (yes/no) and high blood eosinophil count (yes/no) into the model. The increased readmission rate with a high blood eosinophil count was found only in non-smokers (HR 1.84; ~~1.21~~1.20–2.80; p=0.005~~4~~) and not in current smokers (HR ~~0.81~~0.88; ~~0.41~~0.44–1.76~~1.61~~; p=~~0.55~~0.73). In this analysis of all 2,613 patients, 16 patients without recent, recorded smoking status were included as non-smokers (never-smokers plus ex-smokers).

Results were similar for patients with known smoking status, with a significant ~~95%~~216% higher adjusted risk of readmission for never-smokers with high blood eosinophil count, and no additional risk for current smokers with high blood eosinophil count (Table ~~2~~3). Although the association was most pronounced in never-smokers, no significant difference in the association was found between never-smokers and ex-smokers (p=~~0.80~~0.67) in the 2,050 patients recorded as not currently smoking.

Sensitivity analyses

A high blood eosinophil count was recorded for 1,328 patients (51%) when defined as ≥0.25x10^9 cells/L, and for 588 patients (23%) when defined as ≥0.45x10^9 cells/L. The association between a high blood eosinophil count and readmission to hospital for asthma was less pronounced and not significant for patients with blood eosinophil count of either ≥0.25x10^9 cells/L (HR=~~1.16~~1.17; 0.82−1.66~~1.65~~; p=0.39~~0.41~~) or ≥0.45x10^9 cells/L (HR=~~1.12~~1.15; ~~0.75~~0.77−1.72~~1.69~~; p=0.50~~0.57~~; S3 Table). The association was also not significant in never-

smokers or in never/ex-smokers combined using either definition of high blood eosinophil count (S3 Table).

A total of 169 of the 2,613 patients (6%) had no prescription for ICS in the baseline year before being hospitalized for asthma; of the 169, 115 (68%) had ICS prescribed in the outcome year. After exclusion of these 115 patients, HRs for the association with blood eosinophil count of $\geq 0.35 \times 10^9$ cells/L slightly increased as compared with those for the full population (S3 Table). The HR was ~~1.76~~1.77 (95% CI, ~~1.14~~1.15–2.72~~2.70~~; p=0.009~~0.010~~) for never/ex-smokers combined, which was very similar to the HR for never/ex-smokers combined of the full population (~~1.77~~1.78). However, effect modification by current smokers was not significant in this subpopulation (p=0.28~~102~~).

Results of an additional subanalysis excluding patients with a concomitant diagnosis of COPD showed no relevant difference in association for the remaining 2,329 patients (HR= 1.48; 95% CI 1.01–2.17, p=0.045; see S3 Table).

Discussion

In this large, historical cohort study, we found that patients who had a blood eosinophil count of $\geq 0.35 \times 10^9$ cells/L recorded in the year preceding an asthma-related hospitalization had a significantly greater risk of readmission for asthma during the year after they were discharged. Few patients (n=6) were readmitted to hospital for asthma within 4 weeks after discharge, while by 1 year after discharge, 5% (130 of 2,613) patients were readmitted for asthma. The greater risk of readmission during 1 year follow-up was present only for patients with high blood eosinophil count who were never- or ex-smokers (not for current smokers).

Our study is one of few studies examining hospital readmissions for asthma in a general asthma population and in the real-life setting. Readmissions in the present study were comparatively infrequent relative to results in other studies: for example, in one US study, approximately 4% of patients were readmitted for an asthma exacerbation within 30 days [~~19~~21], and in France from 2002–2005, 15% were readmitted for asthma within 1 year [~~20~~22]. The overall rate of hospital admissions for asthma in England appears to be lower that than for Western Europe as a whole, the latter reported in 2004 to be 7% [1,23].

Other recent studies of hospital readmissions have been limited to patients on systemic corticosteroids [~~8~~9], have examined readmissions up to only 30 days [~~10,11~~11,12,24~~,21~~], were much smaller [~~21~~24], and/or were conducted at a single institution [~~22,23~~25,26]. None of these studies, nor others examining readmissions after 30 days [~~24–26~~27-29], examined the association of hospital readmissions with blood eosinophil count. While Gonzalez-Barcala et al. [13] in their retrospective study at a single hospital in Spain found differently from the present study that elevated eosinophil count was associated with a lower incidence of readmissions, it is difficult to compare their study with ours because of differences in methods. For example, the reference blood eosinophil count was that taken upon admission rather than before hospitalization during a baseline year, and the length of the follow-up period for analyzing readmissions is unclear [13].

An interesting finding in the present study that requires further investigation is the effect of smoking status on association of readmissions with eosinophil count. Cigarette smoking increases levels of oxidative stress, alters airway immune responses, and increases risk of hospitalization in patients with asthma [~~27~~30]. Westerhof et al. [~~28~~31] in their study of patients with severe asthma found that frequent exacerbations were associated with blood eosinophil count only in never smokers and not in ex-smokers, for whom blood neutrophil count was an

independent predictor of frequent exacerbations (smokers not studied). In our study, both never- and ex-smokers (but not current smokers) who had a high eosinophil count were at greater risk of asthma-related readmission, although for ex-smokers separately this association was not statistically significant. Moreover, in our study the difference in association between non-smokers (never-plus ex-smokers pooled) and smokers was large and statistically significant. Clearly, additional work is needed to examine biomarker and peripheral blood cell profiles in relation to smoking status and hospital readmissions and other asthma-related outcomes.

The median duration of hospitalization (2 nights) was the same in both normal and high blood eosinophil cohorts; however, patients with a high blood eosinophil count were less likely to have a hospital stay longer than 5 nights (17% vs. 24% of those without high eosinophil count). This finding illustrates the conundrum of eosinophilic asthma: while it tends to be more severe in terms of exacerbations and asthma control, eosinophilic asthma is also potentially more responsive to therapies targeting type 2 inflammation, including ICS and biologics.

We speculated that the association between eosinophil count and readmission could be diluted for patients with eosinophil count performed several months before the first admission; therefore, we re-examined outcomes including only patients with eosinophil counts measured close to the initial hospitalization to see if the association were stronger. However, when selecting those with eosinophil count recorded within 4 months before hospitalization, the numbers became small and associations non-significant, although the direction of the effect was the same: for never- and ex-smokers pooled (n=915), the risk of readmission was 51% greater but non-significant (adjusted HR ~~1.51~~1.69; ~~0.54~~0.60–~~4.76~~4.25; p=0.32~~43~~).

A strength of this study is that we included a broad patient population with asthma, not limited to those with severe asthma. We selected inclusion criteria to ensure that patients' asthma

was actively managed in advance of the hospital admission, thereby excluding patients experiencing a first episode of asthma diagnosed at the time of admission. Moreover, we required that patients had not received an oral corticosteroid prescription within 2 weeks before the eosinophil count to obviate the eosinopenic effects of systemic corticosteroids [~~29,30~~32,33]. The data sources we used are well-regarded and frequently employed for pharmacoepidemiological studies [~~13-15~~15-17,~~31~~34]. The primary care data in the CPRD is considered to be high-quality, with recording that has been standardized and improved since the institution in 2004 of the UK Quality Outcomes Framework (QOF) [~~15~~17], which provides financial incentives for GPs to deliver quality care, including an annual asthma review covering asthma control status, smoking, and inhaler technique. Detailed information about hospital admissions was drawn from HES, a data warehouse linked to the CPRD [~~14~~16].

Nevertheless, a limitation is that the study dataset comprised information collected for clinical and routine use rather than specifically for research purposes. Moreover, prescriptions for drugs prescribed by specialists are not reliably recorded in the CPRD. Therefore, we could not evaluate treatment prescribed immediately after hospital discharge. However, the daily dose of ICS prescribed by GPs in the year after admission was not significantly different between patients with and without high eosinophil counts (median for both: 329 vs. 329 µg/day fluticasone-equivalent, p=0.70, Mann-Whitney test). Finally, as for all observational studies, there is the possibility of residual confounding from unrecognized and/or unmeasured factors.

A “count-response” association of blood eosinophil levels with risk of asthma exacerbations has been reported in both an observational study [3] and for the placebo arm of clinical trials [~~32,33~~35,36]. Our study had insufficient patient numbers to assess the presence of a count-response relationship with hospital readmissions using incremental categories to define

high eosinophil count. Our definition of $\geq 0.35 \times 10^9$ cells/L for high blood eosinophil count captured a clear association of high blood eosinophil count with risk of readmission, while there were fewer patients, hence limited statistical power, to evaluate the higher cut-point of $\geq 0.45 \times 10^9$ cells/L, although the direction of the effect was the same. Alternatively, new ICS use or better ICS adherence after the index hospitalization might have reduced the effect of elevated eosinophil count; however, it would not be easy to quantify this possibility in the framework of a historical cohort study, and in spite of this possibility we found a strong association at the $\geq 0.35 \times 10^9$ cells/L definition.

We did not exclude patients with a concomitant diagnosis of COPD; therefore, approximately one-tenth of the study population appeared to have some form of physician-diagnosed asthma-COPD overlap [~~34~~37], although these patients were too few to analyze separately. However, the sensitivity analysis excluding these patients supported the findings for the full population.

By necessity we were able to include only patients who had a recorded blood eosinophil count, which is not routinely measured in clinical practice, a factor serving as a possible source of selection bias and thereby limiting the generalizability of our findings. There were large differences in baseline characteristics between the patients with available eosinophil count and those without, who tended to be younger; more likely female, a current smoker, and of normal weight; and less likely having comorbidities such as rhinitis, chronic sinusitis, gastroesophageal reflux disease, and cardiovascular disease. The age differences were expected because older people more frequently have full blood counts available. Further work is needed to examine the use of blood eosinophil count in the clinical assessment of the full spectrum of patients with asthma.

Tailoring asthma therapy using sputum eosinophil counts appears to be effective in reducing exacerbations, particularly for adults with frequent exacerbations [~~35~~38]. Thus, blood eosinophil count, more practical to measure than sputum eosinophil count, could play a role in tailoring asthma therapy with the goal of reducing exacerbations, hence potentially hospital readmissions. Moreover, further research is needed to identify the mechanism(s) behind the increased risk of readmission associated with high blood eosinophil count, such as possible undertreatment with ICS or insufficient effectiveness of ICS. In addition, more specifically, a re-examination is needed of the absence of association with readmissions and high blood eosinophil count in current smokers, as there was limited statistical power in this subgroup of patients, reflected by the wide confidence interval.

Conclusions

A high blood eosinophil count in the year before an asthma-related hospitalization is associated with increased risk of readmission within the following year. This risk was slightly ~~increased~~ greater in the subset of patients who were not new initiators of ICS treatment after their index hospital admission, suggesting that this trait is only partially treatable with anti-inflammatory therapy. This association was present only in non-smoking patients with high blood eosinophil count. Our findings support the benefit of including a full blood count with differential as a routine assessment in clinical practice for patients with not well-controlled asthma. Moreover, our findings support the need for careful follow-up, with treatment optimization, after hospital discharge for patients with asthma and preadmission high blood eosinophil count.

Acknowledgments

Writing and editorial support was provided by Elizabeth V. Hillyer, DVM, supported by the Observational and Pragmatic Research Institute Pte Ltd (OPRI).

References

1. Mukherjee M, Stoddart A, Gupta RP, Nwaru BI, Farr A, Heaven M, et al. The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases. BMC Med. 2016;14:113. doi: 10.1186/s12916-016-0657-8.
2. Zeiger RS, Schatz M, Dalal AA, Chen W, Sadikova E, Suruki RY, et al. Blood eosinophil count and outcomes in severe uncontrolled asthma: a prospective study. J Allergy Clin Immunol Pract. 2017;5:144-53 e8. doi: 10.1016/j.jaip.2016.07.015.
3. Price DB, Rigazio A, Campbell JD, Bleecker ER, Corrigan CJ, Thomas M, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. Lancet Respir Med. 2015;3:849-58. doi: 10.1016/S2213-2600(15)00367-7.
4. Casciano J, Krishnan JA, Small MB, Buck PO, Gopalan G, Li C, et al. Burden of asthma with elevated blood eosinophil levels. BMC Pulm Med. 2016;16:100. doi: 10.1186/s12890-016-0263-8.
5. Kerkhof M, Tran TN, Soriano JB, Golam S, Gibson D, Hillyer EV, et al. Healthcare resource use and costs of severe, uncontrolled eosinophilic asthma in the UK general population. Thorax. 2018;73:116-24. doi: 10.1136/thoraxjnl-2017-210531.
6. Makela MJ, Christensen HN, Karlsson A, Rastogi S, Kettunen K. Health care resource utilization and characteristics of patients with eosinophilic asthma in secondary health care in Finland. Eur Clin Respir J. 2018;5:1458560. doi: 10.1080/20018525.2018.1458560.

7. Yancey SW, Ortega HG, Keene ON, Mayer B, Gunsoy NB, Brightling CE, et al. Meta-analysis of asthma-related hospitalization in mepolizumab studies of severe eosinophilic asthma. J Allergy Clin Immunol. 2017;139:1167-75 e2. doi: 10.1016/j.jaci.2016.08.008.

~~7~~8. Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. N Engl J Med. 2017;376:2448-58. doi: 10.1056/NEJMoa1703501.

~~8~~9. Sadatsafavi M, Lynd LD, De Vera MA, Zafari Z, FitzGerald JM. One-year outcomes of inhaled controller therapies added to systemic corticosteroids after asthma-related hospital discharge. Respir Med. 2015;109:320-8. doi: 10.1016/j.rmed.2014.12.014.

~~9~~10. Suissa S, Ernst P, Kezouh A. Regular use of inhaled corticosteroids and the long term prevention of hospitalisation for asthma. Thorax. 2002;57:880-4.

~~10~~11. Veeranki SP, Sharma K, Ohabughiro MU, Mehta HB, Adhikari D, Kuo YF, et al. 30-Day readmissions in hospitalized adults with asthma exacerbations: insights from the Nationwide Readmission Database. Chest. 2016;150:1162-5. doi: 10.1016/j.chest.2016.07.043.

~~11~~12. Veeranki SP, Ohabughiro MU, Moran J, Mehta HB, Ameredes BT, Kuo YF, et al. National estimates of 30-day readmissions among children hospitalized for asthma in the United States. J Asthma. 2017:1-10. doi: 10.1080/02770903.2017.1365888.

13. Gonzalez-Barcala FJ, San-Jose ME, Nieto-Fontarigo JJ, Carreira JM, Calvo-Alvarez U, Cruz MJ, et al. Association between blood eosinophil count with asthma hospital readmissions. Eur J Intern Med. 2018. doi: 10.1016/j.ejim.2018.02.034.

12~~14~~. Couillard S, Larivee P, Courteau J, Vanasse A. Eosinophils in COPD exacerbations are associated with increased readmissions. Chest. 2017;151:366-73. doi: 10.1016/j.chest.2016.10.003.

13~~15~~. Clinical Practice Research Datalink. (cited April 16, 2018) Available from: http://www.cprd.com.

14~~16~~. UK National Health Service. Hospital Episode Statistics (HES). (cited April 16, 2018) Available from: http://content.digital.nhs.uk/hes.

15~~17~~. UK National Health Service. Quality and Outcomes Framework (QOF). (cited April 16, 2018) Available from: http://www.hscic.gov.uk/qof.

16~~18~~. Roche N, Reddel H, Martin R, Brusselle G, Papi A, Thomas M, et al. Quality standards for real-world research. Focus on observational database studies of comparative effectiveness. Ann Am Thorac Soc. 2014;11 Suppl 2:S99-S104. doi: 10.1513/AnnalsATS.201309-300RM.

17~~19~~. The European Union electronic Register of Post-Authorisation Studies (EU PAS Register). (cited April 16, 2018). Available from: http://www.encepp.eu/encepp/studiesDatabase.jsp.

18~~20~~. Global Initiative for Asthma (GINA). GINA Report, Global Strategy for Asthma Management and Prevention. (cited March 18, 2018). Available from: http://ginasthma.org/.

19~~21~~. Hasegawa K, Gibo K, Tsugawa Y, Shimada YJ, Camargo CA, Jr. Age-related differences in the rate, timing, and diagnosis of 30-day readmissions in hospitalized adults with asthma exacerbation. Chest. 2016;149:1021-9. doi: 10.1016/j.chest.2015.12.039.

~~20~~22. Delmas MC, Marguet C, Raherison C, Nicolau J, Fuhrman C. Readmissions for asthma in France in 2002-2005. Rev Mal Respir. 2011;28:e115-22. doi: 10.1016/j.rmr.2011.09.023.

23. Rabe KF, Adachi M, Lai CK, Soriano JB, Vermeire PA, Weiss KB, et al. Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. J Allergy Clin Immunol. 2004;114:40-7.

~~21~~24. Buyantseva LV, Brooks J, Rossi M, Lehman E, Craig TJ. Risk factors associated with 30-day asthma readmissions. J Asthma. 2016;53:684-90. doi: 10.3109/02770903.2016.1140773.

~~22~~25. Gonzalez-Barcala FJ, Calvo-Alvarez U, Garcia-Sanz MT, Garcia-Couceiro N, Martin-Lancharro P, Pose A, et al. Asthma exacerbations: risk factors for hospital readmissions. Ir J Med Sci. 2018;187:155-61. doi: 10.1007/s11845-017-1633-9.

~~23~~26. Pola-Bibian B, Dominguez-Ortega J, Vila-Nadal G, Entrala A, Gonzalez-Cavero L, Barranco P, et al. Asthma exacerbations in a tertiary hospital: clinical features, triggers, and risk factors for hospitalization. J Investig Allergol Clin Immunol. 2017;27:238-45. doi: 10.18176/jiaci.0128.

~~24~~27. Salamzadeh J, Wong IC, Hosker HS, Chrystyn H. A Cox regression analysis of covariates for asthma hospital readmissions. J Asthma. 2003;40:645-52. doi: 10.1081/JAS-120019035.

~~25~~28. Sheikh A, Steiner MF, Cezard G, Bansal N, Fischbacher C, Simpson CR, et al. Ethnic variations in asthma hospital admission, readmission and death: a retrospective, national cohort study of 4.62 million people in Scotland. BMC Med. 2016;14:3. doi: 10.1186/s12916-015-0546-6.

~~26~~29. Beck AF, Huang B, Auger KA, Ryan PH, Chen C, Kahn RS. Explaining racial disparities in child asthma readmission using a causal inference approach. JAMA Pediatr. 2016;170:695-703. doi: 10.1001/jamapediatrics.2016.0269.

~~27~~30. Polosa R, Thomson NC. Smoking and asthma: dangerous liaisons. Eur Respir J. 2013;41:716-26. doi: 10.1183/09031936.00073312.

~~28~~31. Westerhof GA, de Groot JC, Amelink M, de Nijs SB, Ten Brinke A, Weersink EJ, et al. Predictors of frequent exacerbations in (ex)smoking and never smoking adults with severe asthma. Respir Med. 2016;118:122-7. doi: 10.1016/j.rmed.2016.08.006.

~~29~~32. Kellgren JH, Janus O. The eosinopenic response to cortisone and ACTH in normal subjects. Br Med J. 1951;2:1183-7.

~~30~~33. Fleishaker DL, Mukherjee A, Whaley FS, Daniel S, Zeiher BG. Safety and pharmacodynamic dose response of short-term prednisone in healthy adult subjects: a dose ranging, randomized, placebo-controlled, crossover study. BMC Musculoskelet Disord. 2016;17:293. doi: 10.1186/s12891-016-1135-3.

~~31~~34. Boston Collaborative Drug Surveillance Program. The Clinical Practice Research Datalink. (cited April 16, 2018). Available from: http://www.bu.edu/bcdsp/gprd/.

~~32~~35. Ortega HG, Yancey SW, Mayer B, Gunsoy NB, Keene ON, Bleecker ER, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. Lancet Respir Med. 2016;4:549-56. doi: 10.1016/S2213-2600(16)30031-5.

~~33~~36. FitzGerald JM, Bleecker ER, Menzies-Gow A, Zangrilli JG, Hirsch I, Metcalfe P, et al. Predictors of enhanced response with benralizumab for patients with severe asthma:

pooled analysis of the SIROCCO and CALIMA studies. Lancet Respir Med. 2018;6:51-64. doi: 10.1016/S2213-2600(17)30344-2.

~~34~~37. van den Berge M, Aalbers R. The asthma-COPD overlap syndrome: how is it defined and what are its clinical implications? J Asthma Allergy. 2016;9:27-35. doi: 10.2147/JAA.S78900.

~~35~~38. Petsky HL, Li A, Chang AB. Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults. Cochrane Database Syst Rev. 2017;8:CD005603. doi: 10.1002/14651858.CD005603.pub3.

Supporting information

S1 Table. Definitions Applied for Global Initiative for Asthma (GINA) Treatment Step, Determined Using Each Patient's Last Prescription(s) Before the First Hospital Admission.

S2 Table. ~~Baseline~~ Demographic and Clinical Characteristics of All Eligible Patients with Blood Eosinophil Count ~~During the Baseline Year~~ and of Patients Meeting All Eligibility Criteria Except Availability of Eosinophil Count.[a]

S1 Fig. Distribution of the Number of Days before Hospital Discharge on Which the Most Recent Eosinophil Measurement Was Recorded.

S3 Table. Readmissions for Asthma within 1 Year and Hazard Ratios for Readmission in the High Eosinophil Count Cohort: Sensitivity Analyses.

Review Comments to the Author

Please use the space provided to explain your answers to the questions above. You may also include additional comments for the author, including concerns about dual publication, research ethics, or publication ethics. (Please upload your review as an attachment if it exceeds 20,000 characters)

Reviewer #1: Thank you for conducting this retrospective review of admitted asthmatic patients. It was a pleasure to read.

> **Response to Reviewer #1, Comment 1:** Thank you very much for your review and the positive feedback.

2. Could you please comment on the association between increased SABA use and decreased ICS dosages in the group with increased blood eosinophilia? What do you think this connection is? Your manuscript would be strengthened by exploring this in your Discussion.

> **Response to Reviewer #1, Comment 2:** We have additionally analyzed the correlation between average ICS and SABA daily dose and found a weak positive correlation, similar in patients both with and without high blood eosinophil count (Spearman's rho, 0.31 and 0.37, respectively). Therefore, from Table 1, we cannot conclude that decreased ICS use results in increased SABA use at the patient level.
>
> Although outside the scope of this manuscript, we can speculate about a reason for the slightly higher ICS doses in patients with low blood eosinophil count. Small effects of ICS on peripheral blood eosinophil counts may for example play a role. On the other hand, we know that high blood eosinophil counts are associated with more severe asthma, which could explain the greater use of SABA. This is the conundrum of eosinophilic asthma: it tends to be more severe in terms of exacerbations and asthma control but is also potentially more treatment responsive to T2 therapies including ICS and biologics.

Reviewer #2: REVIEW: 18-12337: Association between blood eosinophil count and risk of readmission for patients with asthma: historical cohort study

1. IMPORTANCE OF THE QUESTION OR SUBJECT STUDIED
An understanding of prognosis of asthma based on blood eosinophils count is very interesting topic for research, which has not been fully explained so far.
The objective is clearly stated.
Mention in the introduction section of some references with contradictory results in asthma patients according to blood eosinophils count could be useful to explain the rationale for carrying out this study. There are some studies where higher blood eosinophil count is related to more hospital admissions (Mäkelä MJ, Eur Clin Respir J. 2018 Apr 15;5(1):1458560.), however other authors show us the contrary (Gonzalez-Barcala FJ, Eur J Intern Med. 2018 Mar 4. pii: S0953-6205(18)30094-3.)

> **Response to Reviewer #2, Comment 1:** Thank you for alerting us to these new publications. We have added them to the Introduction as suggested. The variable associations may relate to the conundrum mentioned in our response to the first reviewer's

second point, now included as an additional point in the Discussion (paragraph 5) with reference to the duration of hospitalization.

ADEQUACY OF APPROACH
In the methods section there are some weak points:
1. It is stated that "patients with asthma who had been admitted to hospital in England". However, the meaning of hospital admission is not clear. What should be clarified is whether admission includes emergency room, hospital ward, intensive care unit or all of them

Response to Reviewer #2, Comment 1: We used the HES (Hospital Episode Statistics) Admitted Patient Care (APC) database, which contains records of patients who were admitted to a hospital ward, including patients who visited an emergency department before admission and patients who were admitted to an intensive care unit. We have now added this information to the Methods section.

2. Patients were included "if they had one or more valid blood eosinophil counts recorded during the year before the hospital admission". However, if the patients have more than one valid blood eosinophil count which one was considered: the higher, the smaller, the mean value, the more recent..? It should be clarified.

Response to Reviewer #2, Comment 2: We used the most recent blood eosinophil count before the hospital admission, ie, closest to the admission, now clarified in the Methods section.

3. It is stated that the timing of blood eosinophil count was considered, but it is not explained how it was done?

Response to Reviewer #2, Comment 3: The likelihood of a blood eosinophil count being recorded was greater at dates closer to the hospital admission. We have now reported the median length of time between recorded eosinophil count and admission (with asthma as the primary diagnosis), which was greater in patients with high blood eosinophil counts than in patients without high counts, but the difference in distribution was not statistically significant (144 days [IQR, 56−250] vs. 131 [58−229], p=0.159). We included this variable as a confounder in the Cox regression model, as noted in the statistical analysis methods and in footnotes for Table 3 and S3 Table.

4. In page 8, line 155, it is stated "Global Initiative for Asthma [18] (GINA) step". I think that the words "of treatment" are necessary after step.

Response to Reviewer #2, Comment 4: Thank you. We have now added "treatment" to GINA step wherever mentioned in the manuscript and supplemental information.

5. The statistical treatment seems adequate
6. Acceptable from an ethical point of view

Response to Reviewer #2, Comments 5 and 6: Thank you.

RESULTS

The results are well presented. However there some weak points too:

7. In table S2 there are data about the patients included and not included. Some statistical analysis to check the significance of the difference between these groups seems necessary

Response to Reviewer #2, Comment 7: We have reworked S2 table, as we discovered upon doing the statistical comparisons that some patients were represented more than once in the excluded column (ie, for additional hospitalization episodes at older ages). Moreover, for this new table we have included baseline characteristics for all patients *at the time of their first hospitalization*, in line with the study analyses, to obtain better insights regarding differences in patient characteristics between included vs. excluded patients (with vs. without eosinophil count). (As noted in the Methods section, we included the first hospitalization episode for patients meeting eligibility criteria.)

Therefore, we included the first hospital admission in the database for the 2,613 patients eligible for the study, regardless of availability of eosinophil counts in the prior year. For 2,076 of these 2,613 patients (79%) this admission was the same as the admission analyzed and reported in the main paper. Instead, for 537 patients (21%), the baseline characteristics refer to those at their first recorded hospitalization, while a later admission (when they had a blood eosinophil count recorded during the prior year) was used for the main analyses. Hence there are differences between baseline characteristics for eligible patients as reported in Table 1 versus S2 Table.

We have now added p-values to S2 Table and have noted that there were multiple statistically significant differences, summarized in the Results section, between included and excluded patients. The age differences were expected because older people more frequently have full blood counts available.

8. There are some important data lacking: the duration of hospital stay is important for readmissions

Response to Reviewer #2, Comment 8: Thank you for this important observation. Please see the hospitalization durations now added as a new Table 2. Although the median admission duration (2 nights) was the same in patients with and without a high eosinophil count, there were fewer patients with a long stay in hospital among those with a high blood eosinophil count. Adjustment for this variable in the analyses resulted in a slightly stronger association with risk of readmission (HR=1.49; 95% CI 1.04-2.13; p=0.029).

We have revised Table 3 (formerly Table 2) and S3 Table, showing results adjusted for duration of the first hospitalization.

9. … and treatment after hospital discharge is very important too

Response to Reviewer #2, Comment 9: Prescriptions for drugs prescribed by specialists are not reliably recorded in the CPRD. Therefore, we cannot provide accurate information on treatment immediately after hospital discharge. However, the average daily dose of ICS prescribed by GPs in the year after admission was not significantly different between patients with and without high eosinophil counts (median for both: 329 vs 329 µg/day fluticasone-equivalent, p=0.70, Mann-Whitney test).

In our sensitivity analysis excluding patients who initiated ICS after hospital admission in the first year of follow-up, we found a slightly increased association of high blood eosinophils with readmissions.

We have included these points and the year-2 ICS doses in the Discussion section.

10. In table 2 the analysis of readmissions is not adjusted by obesity. It could be relevant because the impact of obesity could be different in eosinophilic and non-eosinophilic asthma (Mukadam S1, , J Asthma. 2017 Aug 28:1-6)

Response to Reviewer #2, Comment 10: We have evaluated confounding by BMI by including a variable with categories underweight, normal weight, overweight, or obesity into the Cox regression model and found no relevant (<2%) change in the coefficient for the association between a high eosinophil count and time to the first hospital admission. When including a dichotomous variable obesity (yes vs. no) there was only an 0.07% change in coefficient. The main analyses were therefore not adjusted by obesity or BMI. However, there was relevant confounding in the sensitivity analysis using a higher cut-point. These analyses were therefore adjusted for BMI, as noted in the footnote to S3 Table.

.

DISCUSSION

10. Considering that smokers are included and 31% are 65 years old or more, some doubts emerge about the possibility of inclusion of COPD patients. The accuracy of the diagnosis from primary care should be discussed.

Response to Reviewer #2, Comment 10: We have now performed and added the results and discussion of an additional sensitivity analysis excluding patients with a concomitant COPD diagnosis. We found no relevant difference in association for the remaining 2,329 patients: HR= 1.48; 95% CI 1.01–2.17, *P*=0.045, S3 Table).

11. The significant differences between patients included and not included should be cited as a limitation, and as a possible source of inclusion bias.

Response to Reviewer #2, Comment 11: This fact was indeed included in the Discussion as a factor limiting generalizability of study results, and we have now added the reviewer's point that it could serve as a possible source of selection bias.

12. The readmission rate is quite low. Could the authors explain, at least hypothetically the reason for this result?. Could it be due to some selection bias based on lack of accuracy of diagnosis?. Or could it be due to the inclusion of mild exacerbations treated in the emergency room which didn´t need hospital ward admission?

Response to Reviewer #2, Comment 12: Our understanding is that hospitalization rates for asthma are generally lower in the UK than in other countries. We do not believe that readmission rates were low because of selection bias or other factors, because the HES data are considered to be reliable.

By our calculations, the crude annual admission rate in England is approximately 2.5%, including day cases. (This is calculated from the data presented in the first paragraph of the Introduction: "Approximately 83,000 hospital episodes (including inpatient, day-case, and intensive care episodes) were recorded as related to asthma in England in 2011-2012, representing approximately 3.3 million patients with clinician-reported, diagnosed-and-treated asthma in England during that time.") Instead, according to the earlier global Asthma Insights and Reality surveys (Rabe et al. JACI 2004; 114:40-47), the hospitalization rate in western Europe is 7% and that in the US is 9%.

We have expanded the section on rates of readmissions in the second paragraph of the Discussion accordingly.

13. The conclusions are clear and supported by the data presented.

Response to Reviewer #2, Comment 13: Thank you.

REFERENCES

14. The references are relevant and updated. I think there are a few references lacking

Response to Reviewer #2, Comment 14: We have added the references suggested by the reviewer (new references 6 and 13) in addition to another reference (23) supporting the rates of hospitalization in Western Europe.

GRAMMAR AND STYLE

Writing clear and easy to follow

English language satisfactory

ABSTRACT

Adequate and well structured